Submandibular gland sparing IMRT in locally advanced head and neck cancers: Impact on radiation induced xerostomia

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in partial fulfilment of the requirements for the award of the degree of

DOCTOR OF MEDICINE (M.D.) IN RADIOTHERAPY

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CERTIFICATE

This is to certify that this dissertation titled, **"SUBMANDIBULAR GLAND SPARING IMRT IN LOCALLY ADVANCED HEAD AND NECK CANCERS: IMPACT ON RADIATION INDUCED XEROSTOMIA"** is a bonafide record of the work done by Dr. Pranav Ashwin Shah, in the Division of Radiation Oncology, Cancer Institute (W. I. A.), Chennai, during the period of his postgraduate study for the degree of M.D. (Branch X – Radiotherapy) from 2013-2016 under my direct guidance and supervision.

Date : Sep 30 , 2015 Place: Chennai		Dr. G.Selvaluxmy Professor and H.O.D Division of Radiation Oncology Cancer Institute (W.I.A.) Adyar -Chennai

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Dr.PranavAshwin Shah

SUBMANDIBULAR GLAND SPARING IMRT IN LOCALLY ADVANCED HEAD AND NECK CANCERS: IMPACTON RADIATION INDUCED XEROSTOMIA

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Abstract

Background: Xerostomia is one of the most prominent complications in patients with Head and Neck cancers who receive radiation, as it usually involves delivering a high dose to the salivary glands bilaterally.Xerostomia significantly reduces quality of life (QoL) and only parotid gland sparing has shown inconsistent results in improving xerostomia.

Materials and Methods: This was a prospective study in which locally advanced (stage III/ IV) oropharynx, hypopharynx and supraglottic larynx cases that were treated from January 2015 to April 2015were included. Out of the 37 patients, 17 were included in the study arm(contralateral SMG spared). Parotid gland sparing was done in both the groups. The mean doses of the contralateral parotid and submandibular glands were kept under 26Gy and 39Gy respectively.

Xerostomia outcomes were assessed based on RTOG grading and patient rated xerostomia specific QoLquestionnaire.

Results: The grading for xerostomia(of 2 or higher) at the end of treatment, at 3 and 6 months from commencement of treatment were 76%, 53% and 21% respectively in the study group and 80%, 68% and 54% in the control group. The difference at 6 months was statistically significant($p < 0.009$)

The xerostomia questionnaire scored by the patients at the end of 6 months showed a mean score of 13 in the study arm against a score of 24 in the control arm.

Conclusion: Sparing of the contralateral SMG in a selected group of patients of locally advanced head and neck cancers using IMRT is feasible and results in improvement of overall xerostomia outcomes which ultimately can lead to better QoL.

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CONTENTS

1. INTRODUCTION

Head and neck cancers have been one of the most common malignancies for some time now and hence have garnered attention from various fields of oncology to improve the outcomes after treatment. As of now, the approach for locally advanced head and neck cancers is multimodality treatment. Radiation therapy has become an integral part in treatment of head and neck malignancies, and with improvement in techniques, it is now possible to reduce the acute and late complications related to radiation.

Dry mouth or xerostomia is one of the most common complications seen in patients treated for head and neck cancer that occurs during and after completion radiotherapy. This is attributed to the damage caused to the salivary glands that get included in the radiation fields, which is irreparable. Other than significantly impairing the quality of life (QoL) of patients who are potentially cured of their cancers, it may also leave behind severe long term disorders [1].

The major salivary glands involved in salivation are parotid and the submandibular glands. Since the salivary glands are considered to function as parallel organs with respect to late radiation induced effects [2], preservation of the salivary function can be expected if irradiation of large volumes of the major salivary glands can be avoided.

Although parotid sparing IMRT is now being practised at many centres and has become standard of care [3], sparing of only the parotid glands has inconsistently resulted in improvement of xerostomia [4, 5]. This seems to be attributable to the fact that mucin, an important component of saliva that helps in maintaining a subjective sense of hydration is lacking in the saliva secreted by the parotids.

The sub mandibular glands secrete saliva rich in mucin which influences the subjective feeling of mouth dryness.

Hence, to understand the significance of sparing submandibular glands, it is essential to know the anatomy and physiology of sub mandibular glands, and the effect of radiation on them.

Anatomy:

The human salivary gland system is exocrine type and can be broadly divided into two groups.

i) Major salivary glands - Parotid

- Submandibular

- Sublingual

ii) Minor salivary glands – mucosa of tongue, gingiva and oropharynx

The sub mandibular is located in a space called as sub mandibular triangle.

Boundaries: Superior- Inferior edge of mandible

Inferior- anterior and posterior bellies of diagstric muscle

The submandibular gland triangle consists of the following structures within it – submandibular lymph nodes, facial artery and vein, mylohyoid muscle, and three nerves, namely- lingual, hypoglossal, and mylohyoid.

Major portion of the submandibular gland lies posterolateral to the mylohyoid muscle.

Excretory duct:

Wharton's duct is the main excretory duct that drains the submandibular glandt. It runs above the hypoglossal nerve and inferior to the lingual

nerve. The duct opens in the floor of mouth lateral to the lingual frenulum at the level of lower incisors.

Nerve supply:

Parasympathetic- i) Secremotor fibres- facial nerve(CN VII)

ii) Lingual nerve (branch of mandi. division of CN V)

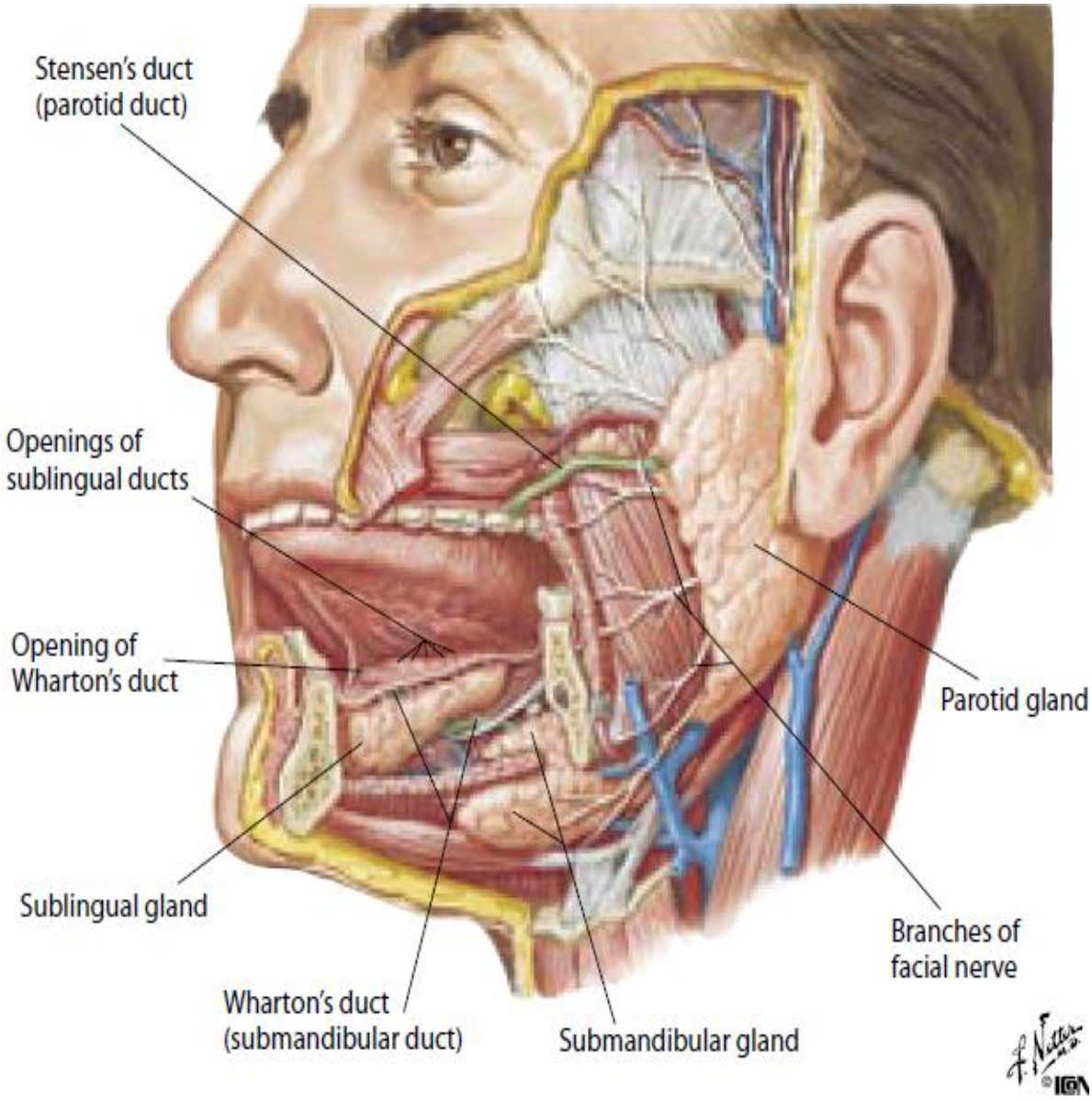
Sympathetic- superior cervical ganglion

Arterial supply- Submental and sublingual arteries (branches of facial and lingual arteries)

Venous drainage- Anterior facial vein → Common facial vein → IJV

Lymphatic drainage- Prevascular and postvascular lymph nodes

Diagrammatic representation of the major salivary glands



Physiology:

The salivary glands are broadly classified into two types based on the type of cells they are comprised of, that is, serous or mucinous or both. Parotid gland mainly comprises of serous cells. On the other hand, submandibular gland contains cells of both serous and mucinous types [6].

Furthermore, salivary secretion is divided into two types- stimulated and unstimulated salivary flow. Most of the stimulated saliva is produced by the parotid glands and while eating, the secretion becomes maximum. Submandibular glands produce almost 90% of the unstimulated salivary output. Unstimulated salivary flow is mainly contributed by the sub-mandibular glands and is at 0.3ml/min [7], which decreases to about half during sleep [8].

There are various factors affecting the salivary flow, and they are different for stimulated and unstimulated flow [10].

FACTORS AFFECTING STIMULATED SALIVARY FLOW:

- Mastication
- Taste
- Olfaction
- Vomiting
- Aging- not clear[9]

The above mentioned factors cause stimulation of salivary flow. Chewing alone can cause increase in salivary flow. But, the stimulation is greater when a person activates both chewing and taste senation.

Of the four basic taste sensations – salt, acid, bitter and sweet; acid is the strongest stimulant of salivary flow [7]. In fact, for measurement of salivary flow during various tests, citric acid is the most commonly used substance to induce flow [11].

FACTORS AFFECTING UNSTIMULATED SALIVARY FLOW:

- Dehydration- decreases
- Smoking- varied
- Posture(sitting/ standing)- increases in standing position
- Drugs

To explain the effect dehydration has on unstimulated salivary flow- just 2% decrease in body weight because of dehydration can decrease salivary flow by 60% [12]. But if there is only a loss 8% of total body water, it can result in stoppage of complete salivary flow [7].

Although, dehydration shows strong correlation with decreased salivary flow rates, serum creatinine and urine osmolality, considered as the standard metabolic markers for dehydration, do not correlate well with flow rates of saliva [13].

Salivary flow rates are the lowest at night, but during daytime they can vary. There is also a seasonal variation seen with flow rates, and they reach their highest during winter. [7, 14, 15].

Smoking has found to show varied effect (increases/ decreases/ no change) on salivation according to different studies [16, 17].

To know the importance of sparing the salivary glands from receiving high dose, it is essential to know the functions of saliva.

FUNCTIONS OF SALIVA [18]

- Lubrication
- Digestion
- Solvent action
- Buffering action
- Remineralization
- Temperature regulation
- Antibacterial/ antifungal action
- Production of regulatory peptides and growth factors

The effect of saliva on swallowing is not as straight forward as the above mentioned functions. Saliva helps in the formation of food bolus by softening the food mechanically and also due to its enzymatic action. It then helps in initiation of swallowing and also aids in lubrication of the bolus to provide a smooth passage.

Although, the patients post radiation therapy complain of difficulty in swallowing, the measurement of bolus transit time and swallowing function did not correlate well [19, 20].

Xerostomia:

Xerostomia has two components - decrease in salivary output along with change in its composition which is objective, and subjective feeling of dryness as reported by the patient. Decreased salivary outflow leads to number of secondary effects that is sometimes called as xerostomia syndrome.

Xerostomia can be divided into two types based on when it is seen from the initiation of treatment.

- Acute/ early (<90days from the initiation of treatment)
- Chronic/ late (>90 days from initiation of treatment)

Permanent or chronic xerostomia is the most common late side effect of radiation therapy for head and neck cancers and is considered by patients as a major cause of decreased quality of life (QoL) [21, 22].

EFFECTS OF XEROSTOMIA:

- Decreased salivary output can affect the taste resulting in reduced taste sensation after completion of radiation therapy and cause a delay in its recovery.
- It is also supposed to contribute to nutritional deficiencies due to difficulty in mastication and deglutition.
- Mucosal fissures and ulceration
- Dental caries and also some infections can be seen as a result of change in the composition of flora in the oral cavity. The risk of osteonecrosis of mandible can increase when there is reduction in the salivary flow [22].

  It may also lead to decreased acid clearance by salivary bicarbonate which can result in oesophageal injury [23].

<u>Xerostomia and mucositis:</u>

Xerostomia and mucositis are common side effects associated with patients undergoing radiation therapy for head and neck cancers.

It has been suggested that xerostomia can predispose the development of mucositis or increase its grade of severity.

This hypothesis is based on

- antimicrobial activity of the saliva
- protective effect of salivary mucins on the mucosa
- secretion of growth factors such as epidermal and fibroblast growth factor in saliva[24].

Few studies where it was found that xerostomia increases risk for mucositis in patients who receive chemotherapy and the decrease in incidence of chemo induced-mucositis when pilocarpine is used[25] support the above mentioned hypothesis.

On the other hand, there are some experiments and clinical obsevations which suggest that the relationship between mucositis and acute xerostomia is more likely to be coincidental rather than causative.

It is more likely that during their initial stages, they occur as independent events. But, during the treatment, reduction in salivary output (protective salivary proteins) may make the mucosa more susceptible to radiation exposure which results in bacterial colonization of the epithelium causing increased and extended mucosal injury.

Pathophysiology of radiation induced xerostomia

Radiation-induced xerostomia begins during the early part of treatment. Salivary flow may decrease by 50 to 60% in the first week.. After 6 to 7 weeks of radiation therapy, flow decreases to approximately 20% [26].

Studies have shown that patients receiving RT; during the first two weeks of treatment, a rapid fall in salivary flow is seen [27].

After completion of 2 weeks of RT, at about 20Gy, only 20% of the original flow of saliva is retained by the major salivary glands. Even after 6 weeks of radiation, recovery did not seem to occur. Compared to the other salivary glands, the parotids lost more of its function- losing its flow to almost 0% whereas the other salivary glands retained up to 20% of their salivary flow [28, 29, 30].

However, it was noted that the difference in radiosensitivity of parotid and submandibular glands was clinically insignificant [31].

In the early part of 20th century, an eminent radiobiologist, Bergonie had described the radiosensitivity of salivary glands difficult to understand [32]. This was because the acinar cells/ excretory or functional cells of the salivary glands were highly well differentiated and had a slow turnover but responded like acute responding tissues to radiation. Tissues with slow mitotic rate have less radiosensitivity.

HYPOTHESES FOR RADIOBIOLOGY OF SALIVARY GLANDS

- The first concept that was suggested was the granulation hypothesis which stated that the membranes of secreting granules in acinar cells are damaged by lipid peroxidation which is induced by radiation. This results in leak of proteolytic enzymes from granules which caused immediate lysis of cells [33].

  However, a study was done early after radiation in which salivary gland scintigraphy (SGS) was performed and it showed that there was no effect on trapping of technetium-pertechnetate, although there was severe reduction in saliva excretion [34]. This finding seemed to indicate that though the excretory function was impaired, the gland volume was not affected. So, cells of the salivary gland producing saliva did not disappear but lost their function during the first few days of radiation.

- Two separate mechanisms were proposed by Konings et al to explain radiation induced salivary gland dysfunction.

  - First, because of selective membrane damage, there is a defect in cellular functioning which impairs the receptor mediated signalling pathways of water excretion. No immediate cell death or lysis takes place.

- Late damage is explained by classical cell killing of progenitor cells and stem cells, thus inhibiting proper cell renewal, and by damage to the cellular environment, causing a shortage of properly functioning secretory cells [35].

The decline in salivary function continues up to several months after radiation therapy [36]. Till 12 to 18 months after radiation, some recovery is possible which depends on the radiation dosage of the salivary glands and the volume that was included in the treatment fields. However, in many cases, xerostomia becomes an irreversible, problem which last for life [37, 38].

Braam et al reported that even many years after radiation, there still could be recovery salivary output, with an increase of about 32% in the flow from 1 to 5 years after completion of treatment [39].

This is not generally accepted, and most studies have shown that over a period of time, there was little recovery in the patients who did not receive some sort of radiation technique where salivary gland was spared [40]. After treatment of head and neck cancers, the prevalence of xerostomia relates to the high radiosensitivity of the salivary glands. During the first week of radiation, after about 5 to 10Gy, saliva production decreases by 60 to 90% with recovery seen later if the radiation dose is moderate [41, 42, 43].

EFFECT OF RADIATION ON SEROUS AND MUCINOUS GLANDS

The mechanism by which damage occurs to acute salivary function is not clearly understood.

The cells of parenchyma of salivary glands have low mitotic activity. It is unlikely that DNA damage which results in reproductive death is soccurs during and just after completion of radiation.

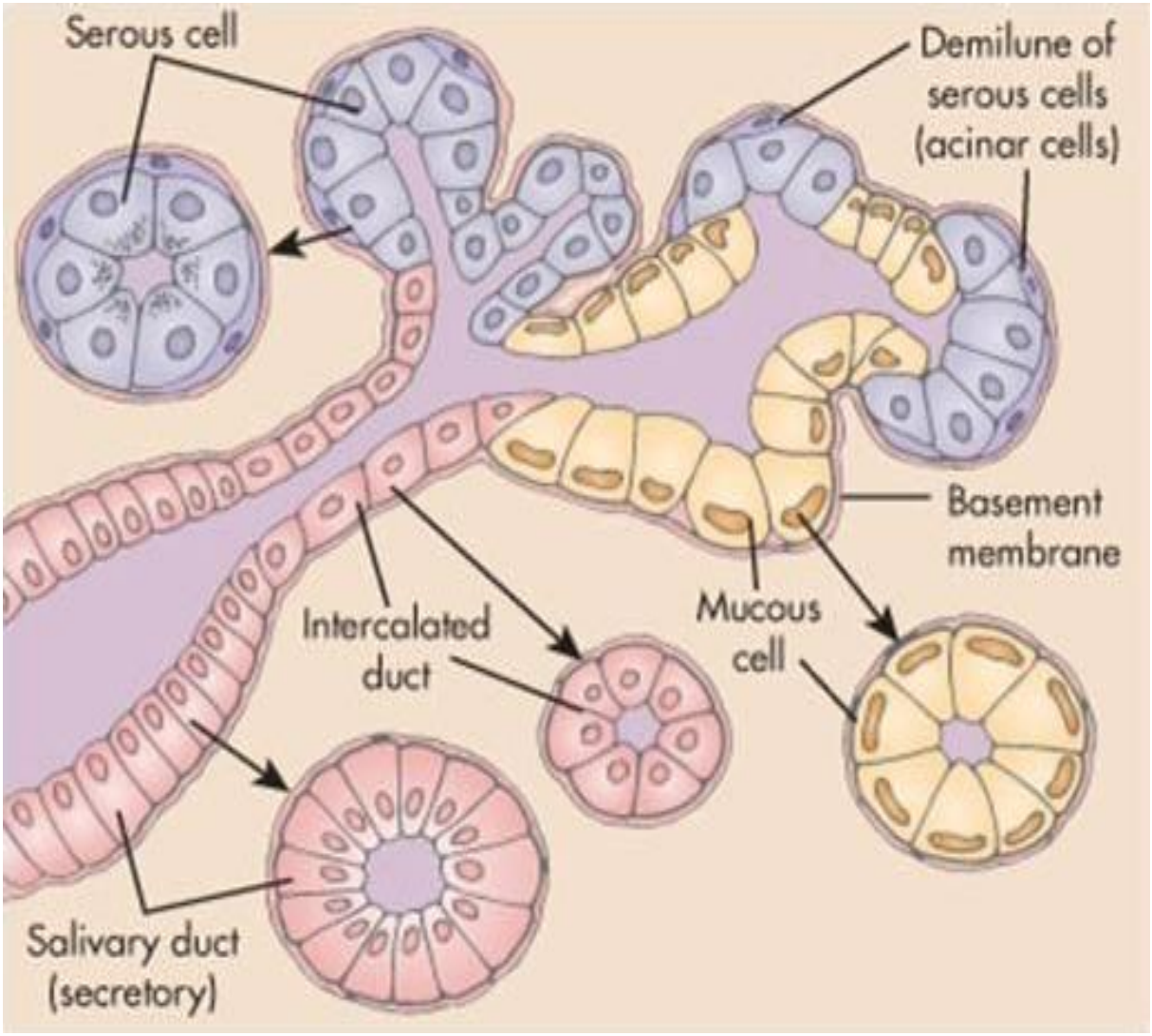
Acute inflammatory infiltrates are seen along with degenerative changes in parenchymal cells as early as 24 hours after the first radiation dose. This is more pronounced in serous compared to mucinous cells [44].

As the radiation dose increases over a period of time and the dose accumulates, the degenerative changes increase over a period of time, and the glands become atrophic and fibrotic. It was observed by Stephens et al in primates' glands that degenerative changes increase in intensity with dose and time, mainly in the serous acinar cells [45]. Two types of damage were described: apoptosis at low doses and at high doses, necrosis [46].

The reduction in watery content of saliva seen initially is attributed to the serous acinar cells because of their high sensitivity to radiation. Relatively, its mucin content, other proteins and minerals remain stable. So initially, there is an increase in concentration of these contents.

Soon after the radiation starts, the salivary secretion is sticky due to initial reduction in its watery content. Mucinous contents of the saliva also diminish over time, and resulting in disappearance of the sticky saliva.

Image showing the different type of cells in the submandibular gland



- The serous cells are more sensitive to radiation effects resulting in decerease in the watery content of the saliva initially
- Mucous cells eventually also are affected causing decrease in the mucinous salivary content.

Measuring Xerostomia

To properly assess the severity of xerostomia, measurements that can be done with accuracy and reliability are required as it also helps in knowing about its time course and dose response relationships. This will also help in assessing the efficacy of measures to be taken to protect the glands or stimulate salivary production after irradiation.

Currently available measurements of xerostomia include

(1) measuring gland activity using functional imaging

(2) measuring salivary output

(3) observer- rated grading of toxicity

(4) instruments that assess patient- reported xerostomia- related symptoms.

Salivary Gland Imaging

Scintigraphy with 99M Tc pertechnetate can be used to image the functional activity of the salivary glands.

It gives information related to the uptake, concentration and the excretory phase of salivation. Here, uptake means the movement of fluid from serum to the glands. The movement of saliva and its modification when it passes from the duct system to the mouth defines excretory phase. Using scintigraphy, the affect radiation has on various phases of gland activity can be deciphered.

It has also been shown that the results obtained through scintigraphy and measurements of salivary output have reasonable correlation [47].

When combined with SPECT (short for single photon emission tomography), it can not only provide spatial information about the anatomical volumes of glands but also give information about response of the salivary glands to different radiation doses, something that cannot be done using other methods [48].

The downside for this method is the technical complexity of the procedure and need for a separate department of nuclear medicine. Hence, for routine clinical assessment of xerostomia, use of scintigraphy is not in practice.

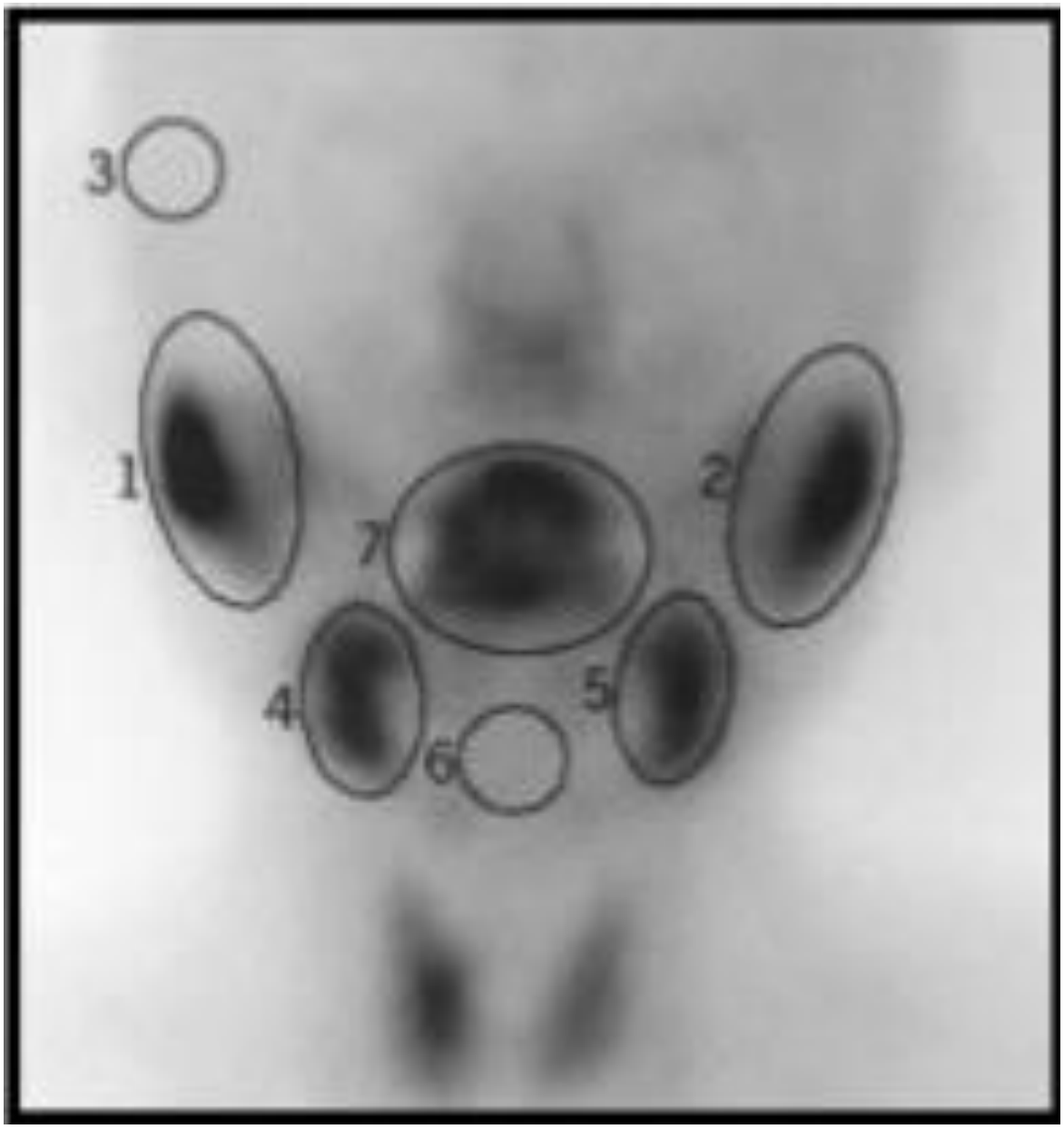


Image showing uptake in the salivary glands after Salivary gland scintigraphy(SGS)

1, 2- parotid glands 4, 5- submandibular glands

7- oral cavity

3- background for parotid glands

6- background for submandibular glands and oral cavity

Salivary Output Measurements

The most commonly used measures to grade xerostomia objectively are measurements of salivary output.

These include - collections of unstimulated saliva

- collections of stimulated saliva which represent salivary output during eating
- whole mouth saliva
- or selective output from each gland

SALIVARY COLLECTION:

Saliva is usually collected over a period of 5 minutes.

a) Collection of whole saliva- This is done by spitting into a container, drainage of the saliva or by measuring the weight of cotton rolls that are inserted in the mouth.

To stimulate, the commonly used method is application of citric acid (2%) which is a strong stimulant, to the dorsum of the tongue or, by chewing which causes mechanical stimulation. The weighing of the collected saliva is done and then the volume is determined with an assumption that the specific gravity is 1, and finally the rate of saliva flow is calculated in mL per min.

b) Selective collection of parotid gland saliva- This is either done by placing a catheter in the parotid duct or, using a suction cup.

The suction cup has a central chamber into which the saliva flows and its outer chamber is used to apply suction so that the cup adheres to the buccal mucosa.

c) Collection of submandibular/ sublingual gland saliva- This can be done by similar methods used to collect parotid gland saliva but the suction is performed on the gland orifices over the floor of the mouth.

There is no method that has proven to be satisfactory for selectively measuring the function of minor salivary glands after RT. For patient's suffering from Sjogren's syndrome, there are reports which have shown methods for measurements of minor salivary gland output from the lip mucosa.

However, in irradiated mucosal surfaces, the flow from minor glands residing over these surfaces have high likelihood of being affected by the parotid and submandibular secretions.

Drawbacks: The results of salivary output measurements obtained by different methods may not be comparable in different studies. This is because of the differences in the collection methods and their duration,

the type of stimulants used and period of time for which they were applied [46].

There are other factors which may affect output of saliva that might be neglected and are supposed to be standardized, like, the variation in salivary output during daytime, effects of posture and effects of hydration.

CHOICE OF SALIVARY COLLECTION METHOD

Based on the investigation or the test that is being performed, the method of saliva collection varies.

Whole saliva may not be only the sum secretions of individual major gland. This is as it is admixed with secretions of minor salivary glands and many non salivary components. Bacterial products, food particles that have been left behind, desquamated cells and debris form the non salivary components. Some of the saliva may be bound to surface of the mucosa [50].

Hence, studies of dose/ response relationships of the salivary glands are considered most reliable when selective salivary gland measurements are performed or when SGS is used.

On the other hand, when general xerostomia or the relationship between the salivary output and symptoms produced are being studied, measuring whole saliva is usually considered as satisfactory.

Unstimulated saliva measurements are the eaiest to perform.

However, they are very sensitive to the hydration status of patients, which may be vary drastically in certain conditions like the weight loss seen in patients during and shortly after radiation, and use of medication that induce xerostomia [51, 52].

Stimulated whole-mouth saliva depends on the type of stimulus used and duration for which it was applied. For comparisons, both interpatient and interstudy, a standard method of collecting saliva is essential.

Navazesh et al has given detailed guidelines for collection of saliva [53].

METHODS/ PRACTICES TO BE FOLLOWED FOR SALIVA COLLECTION

- Ideally, the patient should not eat or drink, or even gargle/ brush for a minimum of 2 hours before collection.
- Collection in the morning is preferable, as the saliva production varies during the daytime physiologically.

- To make sure that the saliva moves to the anterior part of the mouth, the person is made to sit with a slight forward tilt of the head.
- After swallowing the initial saliva, it is allowed to be drained along the lower lip into a funnel, which is placed in a container.

  At the end of the collection period (5 minutes), the subject expectorates residual saliva from the mouth.

The drugs taken by the patient should be noted, and those which may affect the salivary output should be taken into account. This is helpful in studies that use output of saliva as an endpoint or a variable.

There have been several studies that have included measurements of salivary contents like mucins, pH, proteins and inorganic solutes after radiation therapy.

However, there were large inter-individual variations and due to lack of correlation with other aspects of xerostomia these factors are not routinely used for saliva assessment in studies [54].

Observer assessed toxicity rating

The most commonly followed xerostomia rating that is observer based in that proposed by the RTOG.

RTOG Grading System for Xerostomia

A. Acute (within 90 days from the commencement of RT)

Grade 1: Slightly thickened saliva, additional fluids may be required

Grade 2: Thick, sticky saliva. Alteration in diet is required

Grade 3: Inadequate oral nutrition related to salivary gland changes

Grade 4: Acute salivary gland necrosis

B. Chronic (Beyond 90 days from the commencement of RT)

Grade 1: Slight dryness of the mouth; good response to stimulation

Grade 2: Moderate dryness of the mouth, poor response to stimulation

Grade 3: Complete dryness of the mouth; no response to stimulation

Grade 4: Fibrosis

The RTOG scoring criteria of xerostomia has been divided into acute and chronic.

Acute xerostomia (occurring within 3 months of commencement of therapy) is graded primarily based on symptoms

- degree of dry mouth
- thick saliva
- altered taste

Chronic xerostomia (occurring 90 days after initiation of RT) scale is graded based on

- degree of mouth dryness
- response to stimulus.

It is not stated whether these are observer rated or patient reported. Also, the response to stimulus is not defined.

Grade IV which is acute salivary gland necrosis or late salivary gland fibrosis is observer rated.

Hence, this grading system has disparities that need to be sorted out and proper validation of this grading system has not been done.

LENT-SOMA scoring system of xerostomia [55]

This is a more extensive scoring system which includes several paramateres.

- Subjective grading consisting of an evaluation of dryness and whether it is debilitating or not;
- Objective findings of mucosal moisture
- Management issues like the frequency of saliva substitutes, which are highly dependent on patients' threshold to symptom
- Salivary flow relative to the pretreatment flow. Arbitrary cut off values of salivary flow rates relative to the pre-RT flow rates were assigned to the various grades.

The main drawbacks/ deficiencies of these scoring systems include

- information regarding who does the grading is vague

- lack of clear boundaries between the grades (eg, whether dryness is mild or moderate or whether it is moderate or complete),

- salivary flow reduction to different grades has been arbitrarily assigned

Xerostomia Symptoms and Related QOL Assessments

Xerostomia/ dry mouth is a symptom and so, the patient's reporting of the extent of severity is the most vital factor that needs to be assessed and scored. To properly grade/ rank the severity of xerostomia, it is mandatory to develop an instrument that allows its scoring with reliability and which is also sensitive.

A simple question regarding mouth dryness will not cover the various aspects of xerostomia. Therefore, development of many instruments with several questions has been done.

Typically, the xerostomia questionnaires include questions pertaining to the difficulties related to xerostomia that the patients have to rate which are related to chewing, swallowing, talking, and sleep and their need to sip water while eating food or at rest. Various methods are applied for scoring each item and then a summary of all the items is made to get a cumulative score.

Some xerostomia-specific questionnaires have been tested to know if they are valid and reliable, as well as consistent and sensitive [56-58].

A few questions related to xerostomia have been incorporated in several comprehensive head and neck cancer-related QOL instruments [59-64].

Tests for these instruments as a whole for validity and reliability have been done, but, separate testing of the questions that are related to xerostomia has not.

In the clinical practice of head and neck cancer treatment, observer-defined toxicity grading is prevalent.

Eisbruch et al - Proposed New Grading of Symptoms and Toxicity

Eisbruch et al proposed a new grading system in an effort to achieve a clinically meaningful separation between the various xerostomia grades.

The grades were defined according to the functional difficulties that xerostomia caused.

Grade 1 xerostomia – causes no disability, grade 2 was defined as dryness which would require additional fluids for swallowing and grade 3 was dryness which caused patients to alter their diet, and interference with sleep, speaking or other daily activities.

Using this proposal of new system to grade xerostomia, it would be easier to set an endpoint that was clear while conducting trials of post-radiation therapy improvement seen in xerostomia.

This could include the reduction in the rate of grade III hyposalivation, which is associated with functional difficulties that are clinically relevant.

IMPROVEMENT OF XEROSTOMIA OVER TIME POST RT

It was found that xerostomia symptoms improve over time, especially if sparing of part of the major salivary glands has been done.

In the study done at University of Michigan, it was found that the xerostomia scores that were reported by patients (who had bilateral neck irradiation) showed gradual improvement when sparing of partial parotid gland was done. This was more pronounced during the second year after completion of radiation therapy. After 24 months, it was found that their xerostomia scores were almost comparable with the patients who had only one side of the neck irradiated [65].

Similarly, another study of intensity-modulated RT for nasopharyngeal cancer showed that patients who had grade II xerostomia during the first year post radiation, improved to grade I or no xerostomia 2 years after radiation therapy [66].

The reasons for the improvement in symptoms may be attributed to the salivary glands that were spared partially being able to increase the saliva production or the patients themselves who were able to adjust over a period of time. This improvement seemed to be continuous. Therefore, separation of xerostomia into acute and late may not be entirely necessary; however, it is important that during the assessment of symptoms, the point of time at which it is being done is defined.

Proposed New Grading System for Xerostomia

A. Subjective

Grade 1: No disability

Grade 2: Dryness requiring additional fluids for swallowing

Grade 3: Dryness causing dietary alterations, interference with sleep, speaking or other activities

B. Objective*

Grade 1: Flow >0.2 mL/min

Grade 2: Flow 0.1–0.2 mL/min

Grade 3: Flow <0.1 mL/min

*Whole-mouth, unstimulated flow rates.

IMPACT OF XEROSTOMIA ON QUALITY OF LIFE (QoL)

The patients treated for Head and Neck cancers with radiation have their QoL post treatment influenced strongly by xerostomia and the other effects it causes.

A survey conducted by Epstein et al in which, 65 patients who had survived for more than 6 months post RT were included.

It showed that 92% of the patients had dry mouth

43% had difficulty in chewing

63% had dysphagia

76% had loss of taste sensation

51% had altered speech

48.5% had difficulty with dentures

38.5% had increased tooth decay

Pain was commonly seen in these patients and interfered with daily activities in 31% of the patients. More than 50% of the patients had mood complaints.

60% of the patients had interference in their social activities because of their physical condition [67].

Mastication/ manipulation: Most patients who develop xerostomia have to adjust their diet due to the difficulty that they experience while eating food, although it is sometimes done unconsciously [68].

It becomes uncomfortable and sometimes painful to masticate and manipulate food in the oral cavity and so most patients need to sip water frequently while they are eating and there is still a chance of food getting stuck in their mouth or throat [69].

Swallowing: Along with chewing, swallowing difficulty is also a problem that these patients have to face. After radiation to the neck, the pharyngeal structures have their mobility decreased in general, which leads to increase in transit time in the pharynx and a delay in closure of larynx [70, 71].

A study was done where swallowing function of patients (a year after completion of radiation) and healthy volunteers was compared.

Patients showed abnormal bolus transport which was found to be significant. It was found that beginning of elevation of hyoid bone happened a little later, compared to the healthy volunteers and that position of hyoid bone was held for a longer time. Consequently, it was also noted that the upper esophageal sphincter opened too early with respect to the when the food bolus arrived [72].

Other changes included

- Reduction in contact of base of the tongue to the pharyngeal wall
- Restriction in motion of larynx
- Impairment in closure of the vestibule of larynx, true vocal folds, which resulted in aspiration [73, 74]

Taste perception: When the mucosa of oral cavity and pharynx is irradiated, damage of taste receptors occurs, which leads to increasing compromise in taste discrimination [75].

Taste may be affected by decrease in salivary output, which often contributes to the slow return of taste perception after radiation therapy. This is mainly observed after 2 months, when sensation of bitter and salt are generally impaired the most.

Although, during the first year, taste sensation recovers gradually, it is observed that even 1 to 2 years after completion of therapy, partial loss is still present [76].

Speech: Difficulty in speech is another complaint commonly present in patients who have developed xerostomia due to radiation exposure [77, 78].

Even after 5 years, patients still perceive that they have problems of speech, find it difficult to be understood, and also diminished intelligibility [79].

Dental caries: There are a number of factors that secondarily increase the risk of dental caries

- The normal flora of the mouth becomes more cariogenic (eg, increased colonization with Streptococcus mutans and Lactobacillus),
- decrease in the pH of saliva
- alteration of immunoglobulis, and
- loss of mineralizing components [80–82].

Osteoradionecrosis: Risk of osteoradionecrosis of mandible may increase due to decreased salivary flow [83].

Oesophageal injury: Xerostomia leads to decreased salivary bicarbonate which can lead to inadequate clearance of acid causing esophageal injury [84]. Ulcers and fissures of mucosa are more commonly seen if the oral mucosa is dry [85].

Xerostomia syndrome: The aforementioned secondary effects caused by xerostomia contribute to the syndrome referred to as xerostomia syndrome.

In the end, these factors can result in decreased nutrition and loss of weight, which can lead to major health issues [86, 87]

Prevention of Xerostomia

Cytoprotectants

For protection of normal tissues from the ill effects of radiation and chemo drugs, many agents have been developed.

Amifostine (WR-2721, Ethyol1), which is a byproduct of the nuclear warfare program, has been recognized as a radioprotector with potential for a long time.

Mechanism of action:

Amifostine enters the bloodstream

↓ Hydrolysed by alkaline phosphatases

Active form WR-1065

↓ Enters nuclei of cells

Scavenges free radicals

↓

Prevents damage caused by radiation to DNA

It has been suggested that normal tissues are protected selectively as the tumour endothelium lacks alkaline phosphatases and the acidic conditions in the microenvironment prevent the activation of amifostine within the tumour [88].

However, from the data gathered from preclinical studies, the results are not clear, and the issue is still contested [89-91].

Brizel et al., a Phase III trial.

This was a randomized study where 303 patients who were treated with conventional radiation therapy for Head and Neck cancer (both postoperatively and as primary modality) were given amifostine every day before radiation (200 mg/m2 intravenously).

Results- The incidence of acute xerostomia grade 2 or higher had significant reduction (78% to 51%) with the use of Amifostine and there was reduction in grade 2 or higher chronic xerostomia from 57% to 34%. The disease control or overall survival was not altered [92].

As the consequence of this study, use of amifostine received approval from the U.S. Food and Drug Administration (FDA). Recently, a follow-up study was published, and it suggested there was reduction in xerostomia even up to 2 years after completion of treatment with the use of amifostine. No difference was seen in local control or overall survival even after 2 years [93].

A recent meta-analysis tried to overcome the problem of detection small differences in survival. It was found that, amifostine caused reduction in the risk of acute grade 2 or higher xerostomia by 76% and the risk was reduced by 67% for late xerostomia in patients who were treated with radiation therapy [94].

It was also found that effectiveness of treatment was not weakened by addition of amifostine.

During Concomitant chemoradiation:

In concurrent chemoradiation, usage of amifostine has been a controversy [95].

There has been no RCT that has shown that there may be an indication for the using amifostine, so it probably should not be done outside a clinical study [96].

Toxicity: Nausea and emesis are common side effects, but usually mild and are effectively controlled with the use antiemetic drugs.

When given intravenously, amifostine increases the risk of transient hypotension but it is not seen with subcutaneous usage [97].

Submandibular gland transfer

Although it is a less wide-spread approach, salivary gland transfer is an option that has been used in patients for prevention of xerostomia.

Jha et al. and Seikaly et al. were the first to propose transfer of one submandibular gland surgically to the submental space, outside the field of radiation [98, 99]. Altough practically, this can be done only for the patients who have been planned for post-op radiation therapy. This is because the transfer is done as part of the surgical procedure.

It is not always easy to predict which patients would require post-op radiation, and few patients may not be willing for further treatment. In few patients, the shielding of the submental space may not be possible due to its proximity to the high risk region.

In the largest study so far, 28% of the total patients (n= 60) who underwent transfer of salivary gland, either did not receive post op radiation or if they did, it was without the relocated gland being spared from radiation [100]. However, after the transfer, all of the relocated survived and were functioning well. There were no complications during the surgery with an average of 45 minutes operative being added.

The results showed that 81% of the patients had no xerostomia/ grade I xerostomia and only 19% had grade II or higher.

A recently updated long term follow up study showed that the salivary flow was normal in 83% of patients even after 2 years of radiation therapy [101]. Other studies have also shown results that were similar; however, transfer of salivary gland should not be done as a procedure in standard practise [102, 103].

Institutional experience with this technique is essential, and the procedure requires careful patient selection with proper assessment of the benefit that the procedure may give.

Without proper experience, it is highly probable that many of the patients undergoing the procedure will do so without gaining the actual benefit.

Salivary gland sparing RT- parotid

The damage caused by radiation depends on the volume of tissue that receives radiation and the dose that it receives. Therefore, the right way of preventing radiation-induced xerostomia would be to see to it that the radiation is focussed on the target volume and avoid irradiation to the salivary glands when deemed unnecessary.

Using 3D Conformal radiation therapy and Intensity modulated radiation therapy, it is possible to spare a part of the parotid in clinical practice [104]. A small portion of the parotid that is located close to the tumour receives high dose of radiation, whereas a low dose is administered to rest of the gland. Parotid sparing has been used in many centres for prevention of permanent xerostomia [105-108].

At the Leuven University Hospital, a relatively simple 3D-Confromal technique (without the use of intensity modulation) has been in clinical practice since 1999 for sparing the contralateral parotid gland [104].

Although it has been tried and implemented to spare the contralateral parotid using this technique, it is not always possible. Patients who have tumours that are placed in the midline or those that cross the midline have to be excluded. Presence of contralateral lymph node metastasis is also a criterion for exclusion.

If these limitations are respected, then the use of 3D- Conformal radiation therapy or intensity modulation does not cause increase in risk of tumour recurrence in the region that was spared.

There also is evidence that suggests that there is improvement in quality of life with reduction of xerostomia. Lin and colleagues reported that there was significant improvement in both xerostomia and quality of life scores over time during the first year after using intensity modulated radiation therapy [109].

Jabbari et al also conducted a matched case–control study, in which it wa observe that after IMRT, there was improvement in both xerostomia and quality of life with time, but this was not observed after conventional radiation therapy.

The potential benefits gained from IMRT were best observed a little late after completion of radiation (>6 months) [110].

Dose for parotid sparing

The doses and the volumes that can be irradiated to permit preservation of salivary flow after RT have studied and the data is emerging.

Usually, the dose distributions in parotid glands are compared with residual saliva production. This correlation helps in making dose/volume-response relations for function of parotid gland

It has become clear that the relationship between reduction in saliva flow and mean parotid dose for each gland is exponential. This suggests that there is a threshold mean dose for parotid gland that should not be exceeded if adequate gland function has to be retained [111].

Literature support: Eisbruch et al proposed a mean parotid dose of <26 Gy as a dose constraint that had to be met if adequate function was to be retained [112].

A study done in Washington University also reported similar results. It was shown in their results that, if the mean parotid dose exceeded 25.8 Gy, it would likely decrease the flow of saliva to 25% of its flow before commencement of treatment.

The reduction in the incidence of xerostomia was significant when the mean parotid dose of at least one gland was kept below 25.8 Gy [113].

There have been studies where SGS (Salivary gland scintigraphy) was used to assess parotid function after radiation and similar results were reported: a mean parotid dose which did not exceed 26 to 30Gy allowed retention of salivary gland function [114].

Hence, it was concluded that if a mean parotid dose of <26 to 30Gy was used as a planning objective, significant reduction in xerostomia could be achieved [115].

2. LITERATURE REVIEW

1. Saarilahti et al [107]

This was the first study that checked for the feasibility of submandibular gland sparing IMRT.

The study was done in 2006, and it had 36 patients included in whom parotid sparing was done. In a subset of 18 patients, where the risk of recurrence in the region of submandibular gland was judged to be low, full dose of radiation to the contralateral submandibular gland can be spared.

Then, the salivary flow rates- both total unstimulated and stimulated were measured and monitored over a period of time and the adverse effects that were seen were also recorded.

After a follow up period of twelve months following IMRT, the salivary flow rates were measured and it was found that the mean unstimulated saliva flow was 60% of the upfront value among patients who had submandibular gland spared along with parotid sparing and it was only 25% among those who had no sparing of submandibular gland (P=0.006). It was also reported that patients in whom was sparing done had lesser grade two or higher xerostomia, 4 against 11 with a p value = 0.018.

They were also lesser dependent on salivary substitutes.

After a mean follow up period of 31 months, there was no cancer recurrence detected in the vicinity of the spared submandibular glands.

Hence, it was concluded that in a selected group of patients, sparing of submandibular gland could be safely done and it was effective in reducing/ preservation of radiation induced xerostomia.

2. Little et al [133]

This was a prospective study in which assessment of xerostomia was done in patients with head and neck cancers treated with radiation along with concurrent chemotherapy when along with sparing of the parotids using IMRT, dose to other salivary glands was also reduced.

There were 78 patients included in this study where Stage III-IV oropharynx/ nasopharynx cancer underwent chemo-radiation and sparing the parts of the bilateral parotids, minor salivary glands in the oral cavity, and contralateral submandibular gland outside the target (in cases where the contralateral level I region was not at risk). Validated patient-reported xerostomia questionnaire scores and observer-graded xerostomia scores were recorded before the treatment and periodically over a period of 24 months. Stimulated and unstimulated saliva flow rates were measured selectively from parotid and submandibular glands. The mean oral cavity dose acted as a replacement of minor salivary glands function.

On multivariate analyses, after adjusting for the PG and SMG doses, the OC mean dose ($p < .0001$), interval from RT ($p < .0001$), and stimulated PG saliva ($p < .0025$) were significant predictors of the XQ scores and the OC mean dose and time for observer-graded xerostomia. Although scatter plots showed no thresholds, an OC mean dose of <40 Gy and contralateral SMG mean dose of <50 Gy were each associated with low patient-reported and observer-rated xerostomia post treatment,

This study showed that parotids, submandibular glands and oral cavity mean doses were significant in predicting the xerostomia rated by the patients and observer rated findings after completion of chemoradiation. These results supported that efforts to spare all the salivary glands beyond parotids can improve outcomes of xerostomia further.

3. Chajon et al [134]

This study analysed the loco-regional failure patterns in patients with head and neck cancer who were treated using IMRT with parotid, submandibular and accessory salivary glands present in the oral cavity.

Seventy patients with Head and Neck cancers treated by definitive IMRT were included and analysed with a median follow up 20 months.

It was found that the 2 year loco regional control was 76% with one marginal recurrence and in field recurrences were 12 in number. But, there were no recurrences observed in vicinity of spared structures. It was also noted that the loco regional recurrence was not increased by lowering the mean does in the salivary glands but only dependent on the T and N stages.

Taking results into consideration, it seems reasonable to execute treatment plans which can maintain low mean doses of radiation to the oral cavity accessory glands, submandibular along with the patotids.

Sanguineti et al. [135] identified that the risk Level IB involvement even in patients with multiple positive neck levels with early-stage oropharyngeal carcinoma was found to be insignificant.

4. Gensheimer et al [136]

   This had the highest number of patients (n= 114) with locally advanced oropharyngeal carcinoma included in the study till date where contralateral submandibular gland sparing was done using IMRT and the patterns of loco regional recurrence/ failure were studied.

Only locally advanced oropharyngeal cancers were included, to minimize population heterogeneity. Around 90% of the patients were treated with concurrent chemoradiation.

Of the 114 patients included in the study, 76 patients underwent submandibular gland sparing and 38 received unspared IMRT. Among the cSMG spared group, the mean SMG dose was 30.7Gy and the mean parotid dose on the spared side was 22.4Gy.

Xerostomia outcomes were measured at 6, 12 and 24 months from completion of radiation therapy. It was found that in the unspared arm, Grade 2+ xerostomia was 72%, 41% and 36% respectively whereas in the cSMG spared arm, it was 23%, 6% and 3%. This was clinically significant, $p<0.0007$. On multivariate analysis, only cSMG dose and T4 tumors were found to be predictive of xerostomia.

There was no marginal miss or recurrence in the vicinity of the sapred submandibular gland.

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3. AIM OF THE STUDY

This was a study aimed at assessing the clinical advantages achieved with the help of contralateral submandibular gland sparing IMRT. It was a prospective study which focussed on the advantages of reducing the dose received by the major salivary glands- parotid and contralateral submandibular gland. The corresponding changes were observed in the subjective and objectively rated dryness of mouth/ throat at the end of treatment, at 3 months and 6 months from commencement of treatment.

The focus was on reducing the volume of the parotid gland to less than 30Gy and the contralateral submandibular gland to less than 39Gy without comprising the dose delivered to the target area.

The primary end point of this study was to analyze the subjective feeling of dryness based on a patient rated questionnaire and to compare it with patients where sparing of the contralateral submandibular gland was not done. Also, the effect of xerostomia on quality of life (QoL) of the patients was assessed.

The secondary end point was to measure the mean dose received by parotids and submandibular glands in the patients where submandibular sparing was done with the group of patients who were treated without sparing.

4. MATERIAL AND METHODS

This is a prospective, longitudinal study done in patients of locally advanced head and neck cancer patients treated with a curative intent using definitive radiation therapy with/without concurrent chemotherapy (based on patient's fitness). The main objective of this study was to assess the xerostomia of the patients after completion of treatment.

Locally advanced cancers are included in this study as they warrant elective irradiation of bilateral neck and to avoid population heterogeneity which would arise if the early cancers were to be included.

In order to avoid tumour related effects on the end points of this study, the sites of head and neck- oral cavity and glottis larynx were not included in the study.

Oral cavity cancers were not a part as level IB are the first echelon nodes and the sparing of submandibular region is not possible without significant compromise of the dose delivered to the areas at risk. Glottic larynx was avoided as, compared to other sites, the propensity of metastatic lymph node involvement is much lesser due to its poor lymphatic supply [116, 117, 118, 119].

Study period: January to Spetember 2015

Study population:

Inclusion criteria:

1) Oropharynx, hypopharyx and supraglottic larynx cancers
2) Stages III and IV
3) Bilateral neck irradiation required

Exclusion criteria:

1) Early stage (I, II)
2) Recurrent tumors
3) Oropharynx cancer spreading onto the anterior 2/3rd of tongue
4) ECOG PS >2
5) Primary tumor crossing the midline
6) Presence of contralateral neck nodes

Radiation technique:

The principles of target selection and IMRT planning followed are as per the general consensus of target delineation in head and neck cancers (120).

The delineation of the level II region was given importance due to its close proximity to the submandibular gland.

These nodes can be divided into the subdigastric (jugulodigastric) nodes, located below the level at which the posterior belly of the digastric muscle crosses the jugular vein and the more cranially located nodes below the base of skull . The subdigastric nodes are the main nodes involved when contralateral metastasis occurs, whereas the more posteriorly located nodes are at risk bilaterally in cases of cancer of the nasopharynx and in the neck side that contains other Level II-III metastasis [121].

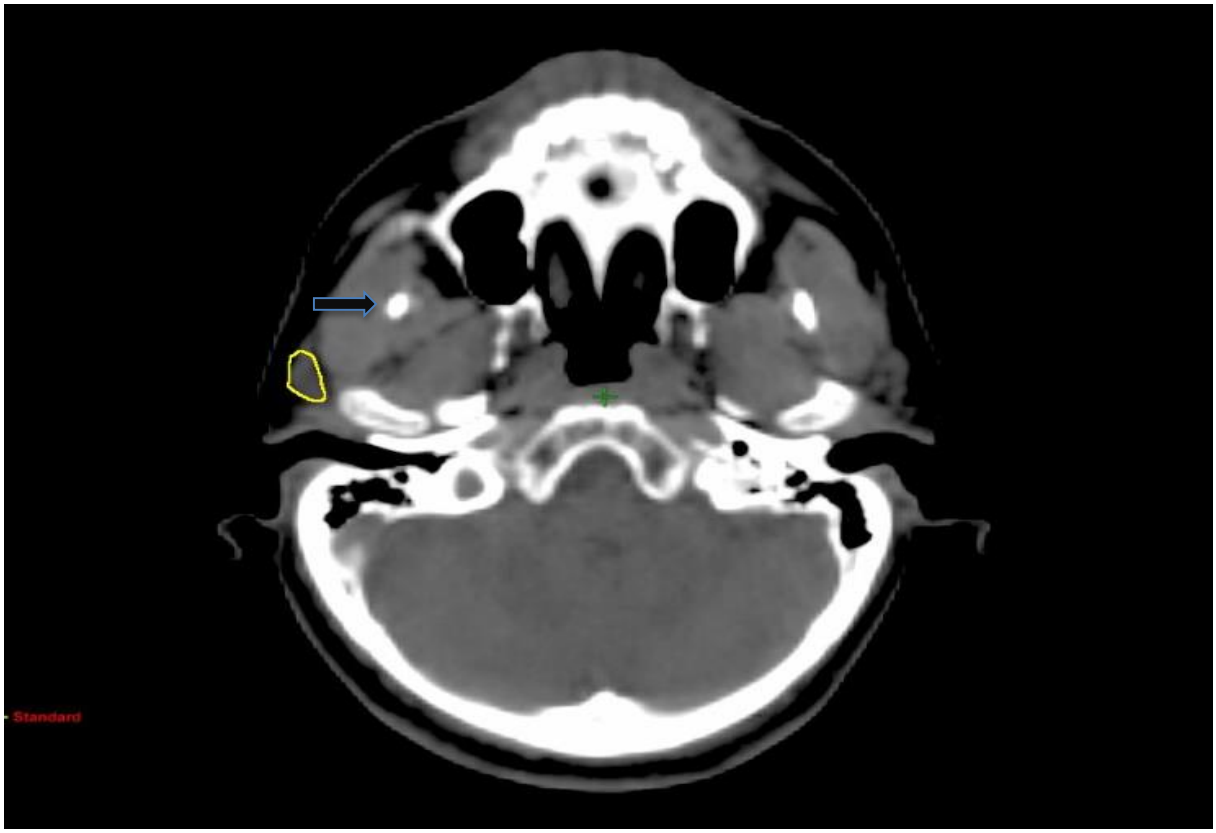
A slightly smaller margin was given on the cSMG spared IMRT plans between the CTV and PTV so that the posterior part of the submandibular gland which forms the anterior border of the level II region does not receive higher dose.

While defining target volumes, the planning target volumes (PTVs) were created using a uniform margin of about 0.5cm from the clinical target volume (CTV) which accounts for the daily setup errors which were monitored based on daily kV portal imaging and not allowed to be beyond 1-1.5mm.

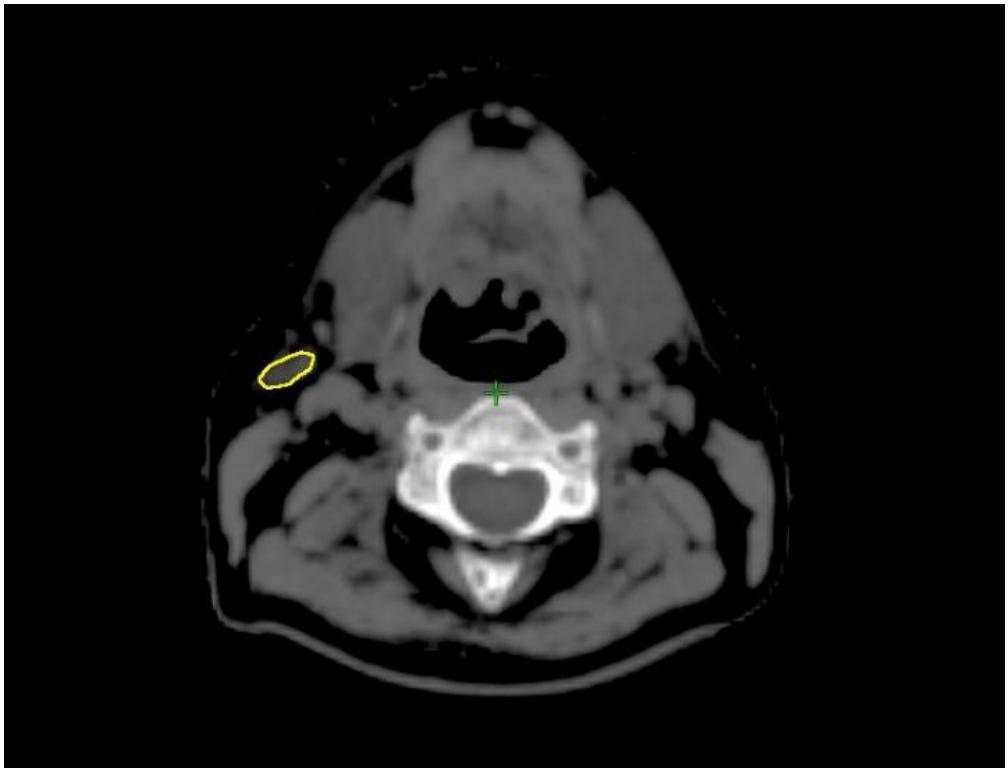
Contouring of the two major salivary glands- the parotids and submandibular glands was given utmost importance and done based on anatomic atlases.

Contouring of the parotid glands

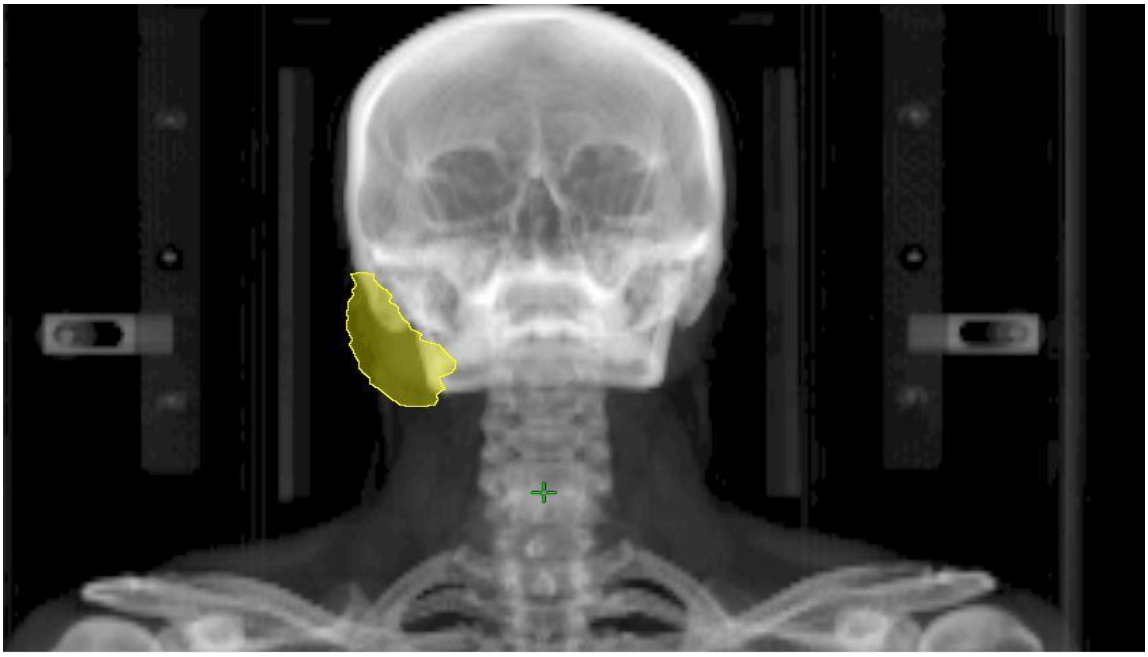
The parotids are the largest set of salivary glands and due to their radiolucency are usually easily picked up distinctly on CT imaging. Its laterally placed position also makes it easy to demarcate the gland based on the structures around it.



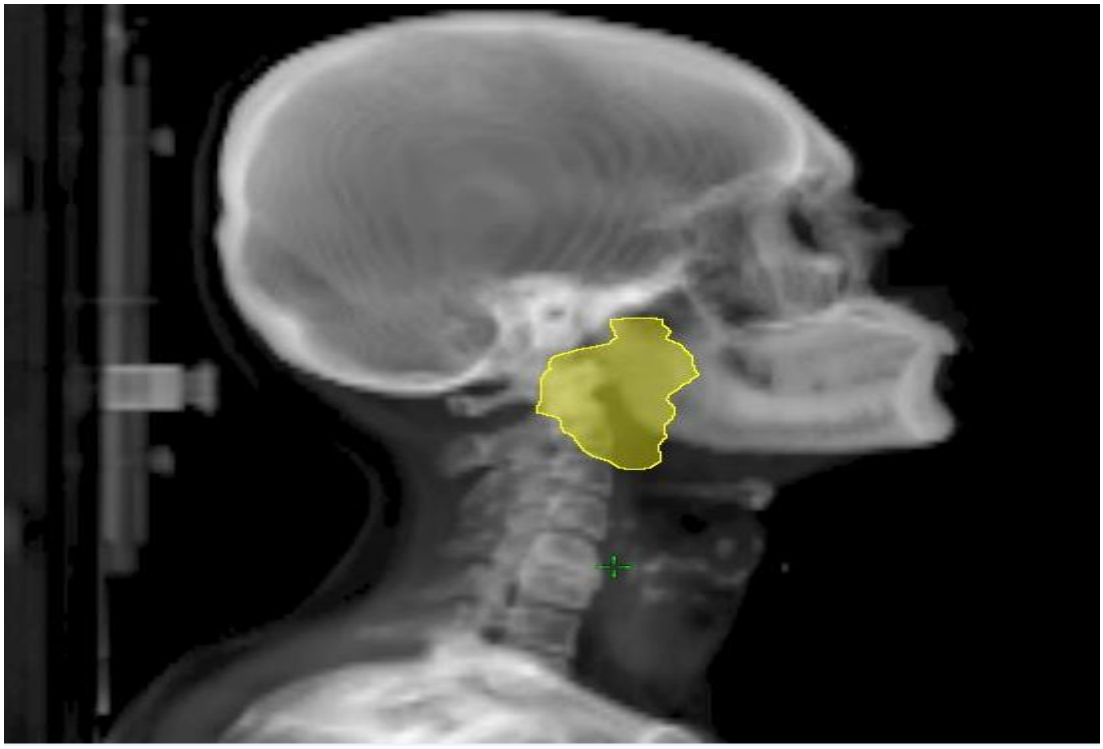
The cranial most part of the parotid gland(orange outline) starts at the level of the mandible(black arrow with blue outline), lies infero lateral to the masseter muscle



The caudal most part of the parotid as seen in the CT cut ends inferior to the submandibular gland and lies superior to the sterno cleido mastoid msucle.



Topographic view of the right parotid- anterior view



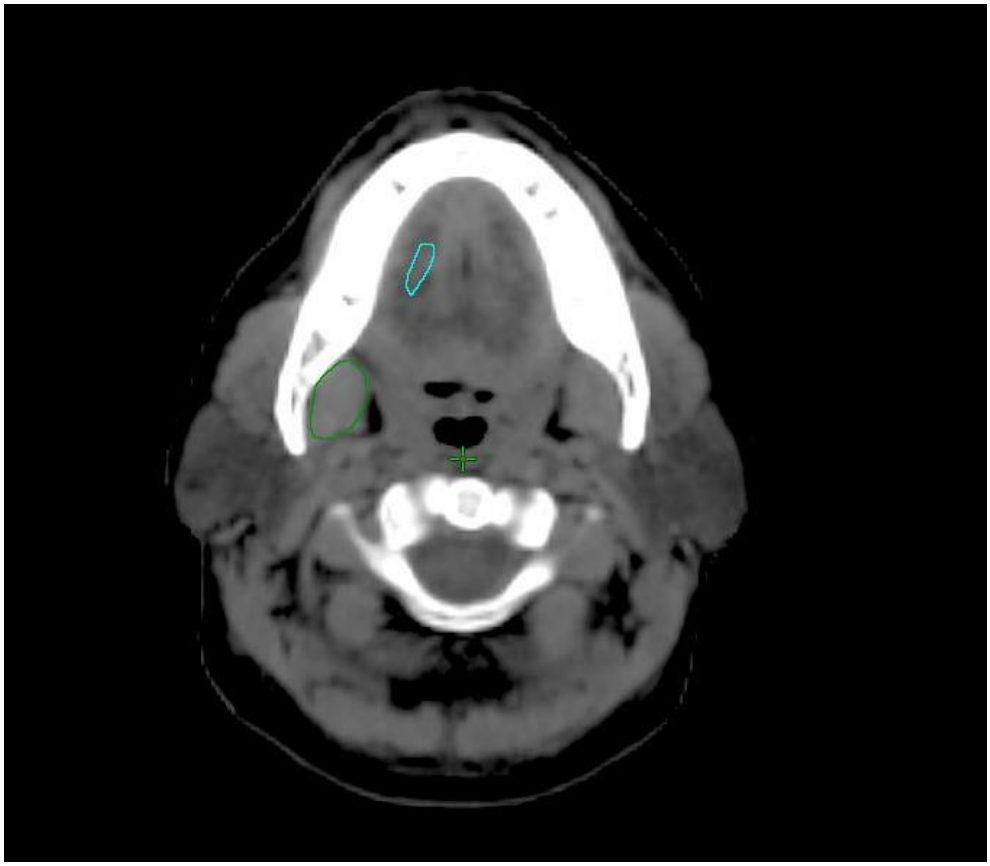
Lateral view- right parotid

Contouring of the submandibular gland

The submandibular glands are the next largest salivary glands and are placed more medially compared. They start just along the level of the ramus of the mandible and then extend inferiorly.

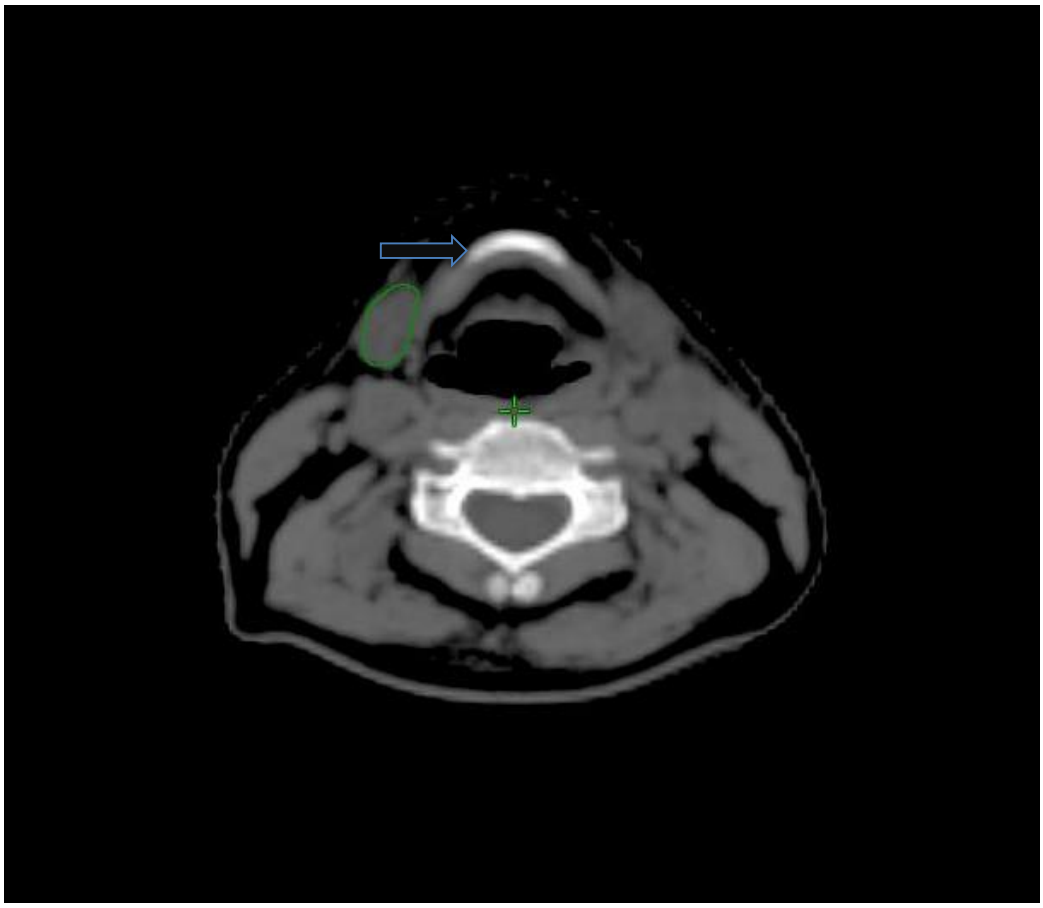
They are a little difficult to demarcate from the adjacent muscle (pterygoid) as they have similar lucency. Hence, an MRI is a better modality of imaging to visualise the submandibular gland,

But, on CT imaging the submandibular gland can be identified based on the anatomic location relative to its adjacent structure, that is, the cranial of the myolohyoid muscle.



The right submandibular gland(green otuline) as seen on this CT cut starts along with the cranial most portion of the mylohyoid muscle(light blue outline).

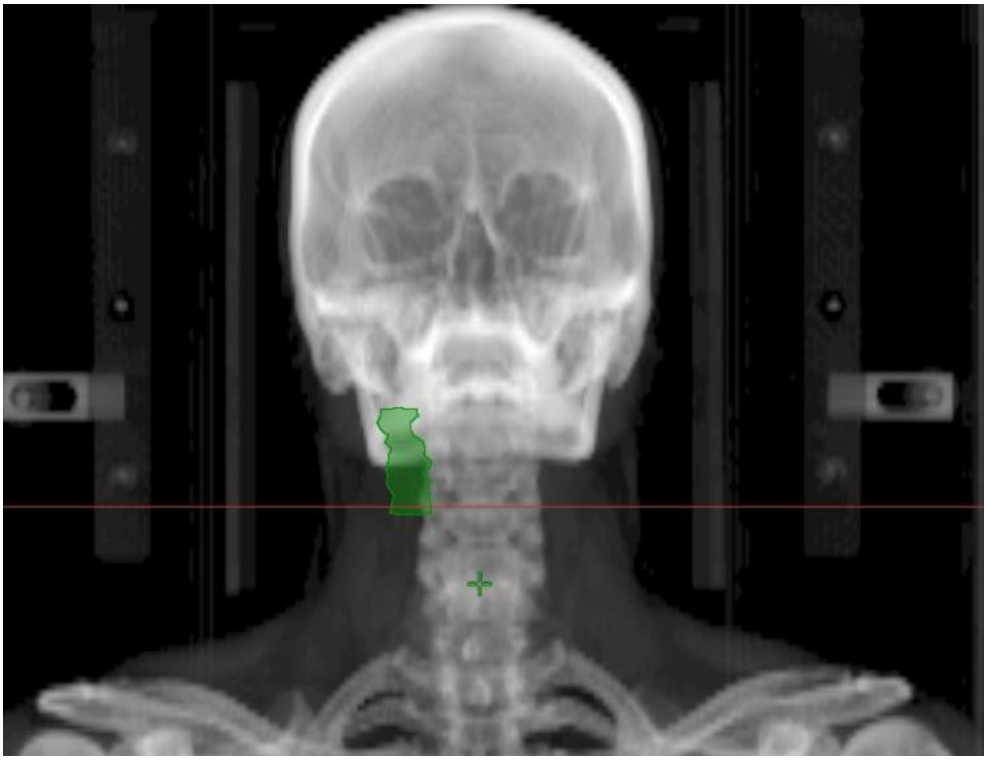
The right parotid is also seen infero-lateral to the submandibular gland with masseter present laterally.



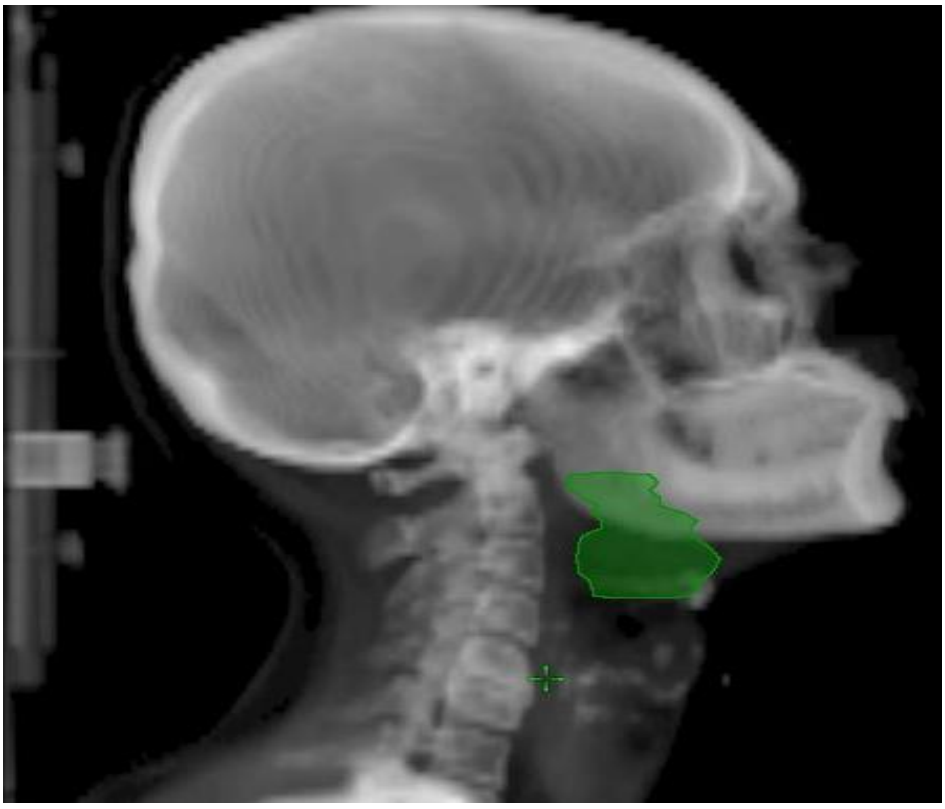
The caudal end of the submandibular gland (green outline) is easier to demarcate as it doesn't have any muscles in close proximity. It ends at the level of the mid portion of the hyoid bone (black arrow with blue outline).

Other anatomic structures around this part of the submandibular are the digastric muscle placed posteriorly and sterno cleido mastoid muscle infero-laterally.

Topographic view of the right submandibular gland- anterior



Topographic view of the right submandibular gland- lateral



Dose prescription

The dose prescription includes all the targets delineated in PTV to receive TD- 60Gy at 200cGy/fraction for five days a week. With the help of in house planning systems (VARIAN), inverse IMRT plans were analysed and executed once target dose homogeneity is achieved. An optimized IMRT plan was thus generated which included the dose given to the delineated PTVs as per the RTOG protocol along with an optimization goal to try and constraint the dose to the swallowing structures. The salivary glands that were contoured were given dosimetric constraints- with the mean dose of parotid gland <30Gy and the mean dose of submandibular gland <39Gy. No compromise to the primary target PTV was allowed while sparing these structures and for achieving optimum dosimetric goals.

In all patients, the prescription dose to the targets was considered as high priority and other critical organ dosimetric constraints were considered to be secondary except for maximal spinal cord dose. The optimized IMRT strategy for sparing of the submandibular gland was implemented and for purpose of the study these dose prescriptions were considered to be clinically significant. For the whole structures and the parts that over lapped the PTVs, DVH analyses were performed and reported.

Dose specifications and constraints used for the two groups

1. cSMG unspared IMRT (control group)

Targets

- PTV60 for the radiological gross disease; prescribed dose 60Gy in 30 fractions

Noninvolved tissues and organs

- Parotid gland, mean dose <26Gy or <50% receive <30Gy
- Maximal dose to brain stem 54Gy
- Maximal dose to spinal cord 45Gy
- Maximal dose to mandible 70Gy

All the non-specific tissues outside PTVs: <1% to receive <110% of PTV60 dose

2. cSMG spared group IMRT(study group)

The dose specifications and constraints given are the same as that for Standard IMRT.

In addition, the constraint for submandibular gland mean dose of <39Gy was also to be followed.

(Abbreviations: cSMG- contralateral submandibular gland, IMRT- intensity modulated radiation therapy, PTV60- planning target volume to which the dose prescribed was 60Gy)

Chemotherapy

- Patients who were deemed as fit for chemotherapy received weekly cisplatin (40mg/m^2) for 5 weeks or 3 cycles of 3 weekly cisplatin (70mg/m^2) along with RT. Patients in whom cisplatin was deferred, would be given weekly carboplatin(AUC 2). If the patient developed toxicity due to chemo which resulted in hindrance to radiation, then the chemo was discontinued.

Supportive care

- Anti-emetics and adequate hydration both before and after chemotherapy was delivered following standard of care.
- Among patients having dysphagia which lead to decreased food intake orally, nasogastric tube intubation was initiated.

Evaluation of xerostomia

All the patients who were part of the study were periodically assessed during the treatment and at the end of treatment, the observer rated grading of xerostomia was done based on the RTOG criteria.

Then, the grading was repeated during the follow up period, 3 months and 6 months after commencement of radiation therapy. This usually coincided with first follow up and the fourth follow up visit.

These scores were systematically noted down and recorded for all the patients who were part of the study and had come for regular follow up.

At the end of 6 months from the commencement, that is, the fourth follow up or when the last recording of the observer rated grading was done, the patients were also given a xerostomia based QoL questionnaire in the language of their preference.

This questionnaire has been developed at the University of Michigan (122).

It consists of eight questions, divided into four questions related to dryness while eating/talking and four related to dryness at rest .The XQ has been found tested for reliability, validated and has been found to be reproducible in measuring patient-reported xerostomia(122, 123, 124). It has been independently validated by investigators at the University of Florida (125).

The Xerostomia Questionnaire (XQ)

1. Rate your difficulty in talking due to dryness ( )

2. Rate your difficulty in chewing due to dryness ( )

3. Rate your difficulty in swallowing solid food due to dryness ( )

4. Rate the frequency of your sleeping problems due to dryness ( )

5. Rate your mouth or throat dryness when eating food ( )

6. Rate your mouth or throat dryness while not eating ( )

7. Rate the frequency of sipping liquids to aid swallowing food ( )

8. Rate the frequency of sipping liquids for oral comfort when not eating ( )

Patients rate each item on a scale from 0 to 5 with 0 being completely normal/least and 5 denoting most difficult/maximum discomfort.

Total score:

The questions 1, 4, 6 and 8 depict the dryness that the patient experiences at rest, and the other questions grade the dryness the patient experiences while eating/ talking.

The maximum score that can be scored is 40.

The scoring was slightly altered for convenience of the patients but the questions and the importance they carried remained the same.

Statistical Analysis

The dose volume effect relationships of all the xerostomia outcome measures and dose values were modeled using multiple regression analyses, with the score of xerostomia using Xerostomia Questionnaire, measured 6 months from commencement of radiation therapy as the dependent variable. Statistical significance was determined at $p \leq 0.05$.

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5. RESULTS

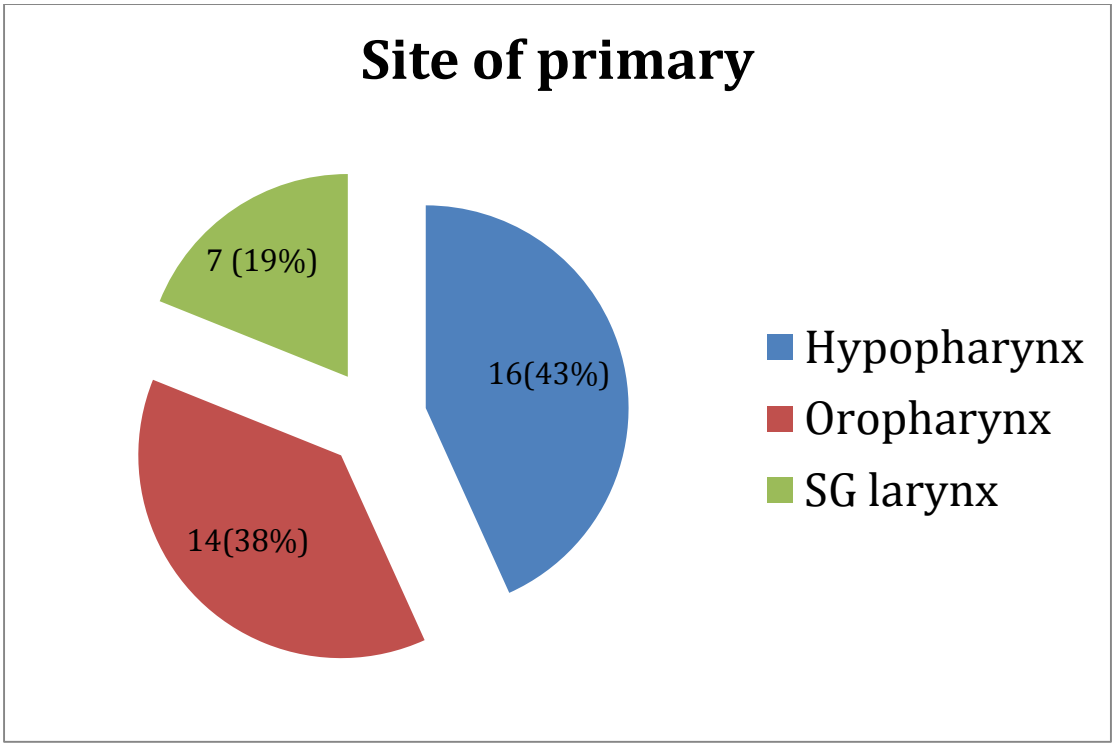
Patient characteristics

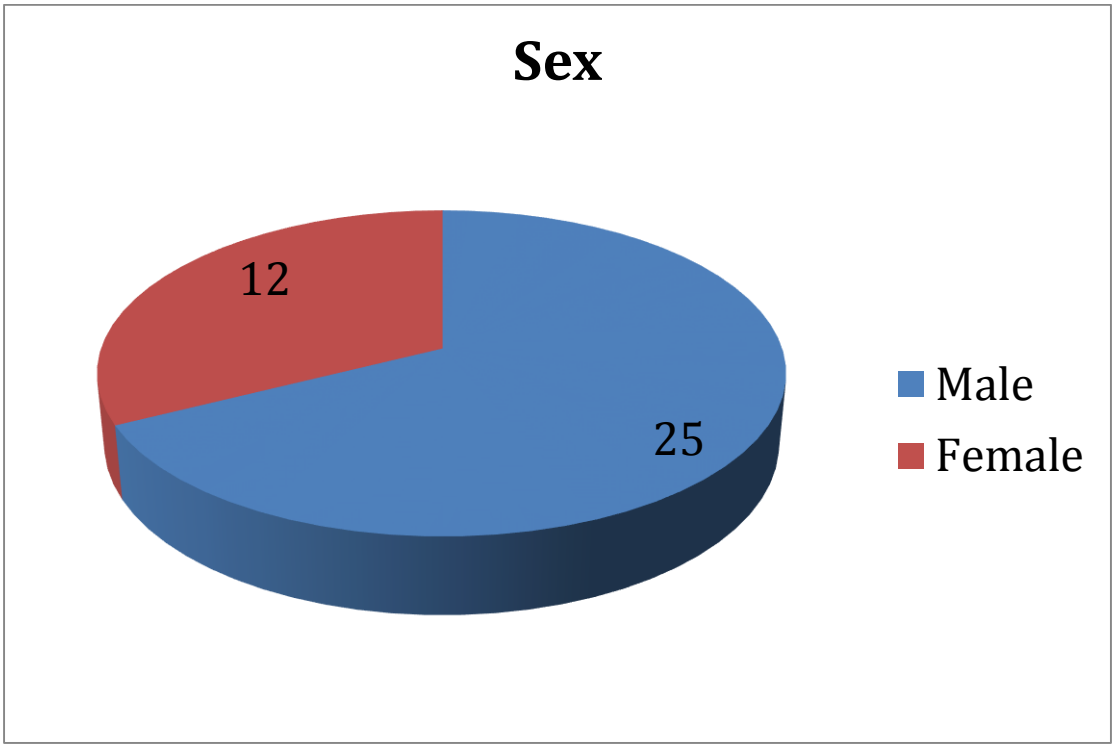
A total of 40 patients were considered for this study, 3 of them defaulted midway through the treatment and so the study was carried forward with the remaining 37 patients. Of these patients, 17 were in the study arm (cSMG spared IMRT) whereas 20 were in the control arm (unspared arm).

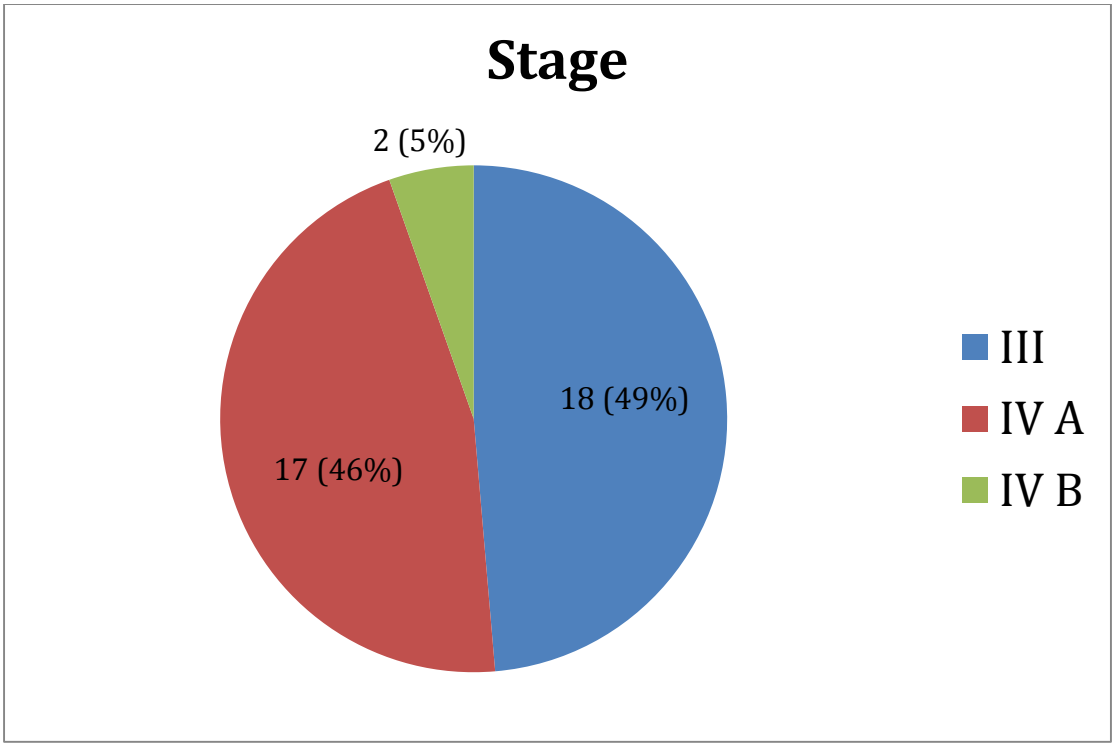
All the patients were locally advanced cancers of oropharynx (14), hypopharynx(16) and supraglottic larynx(7). Male to female ratio in our study was almost 2:1. The mean age of these patients was 59yrs. 26 (70%) out of 37 patients received concurrent chemoradiation with weekly or 3 weekly CDDP (1 patient received carboplatin) and 11 (30%) patients received RT alone.

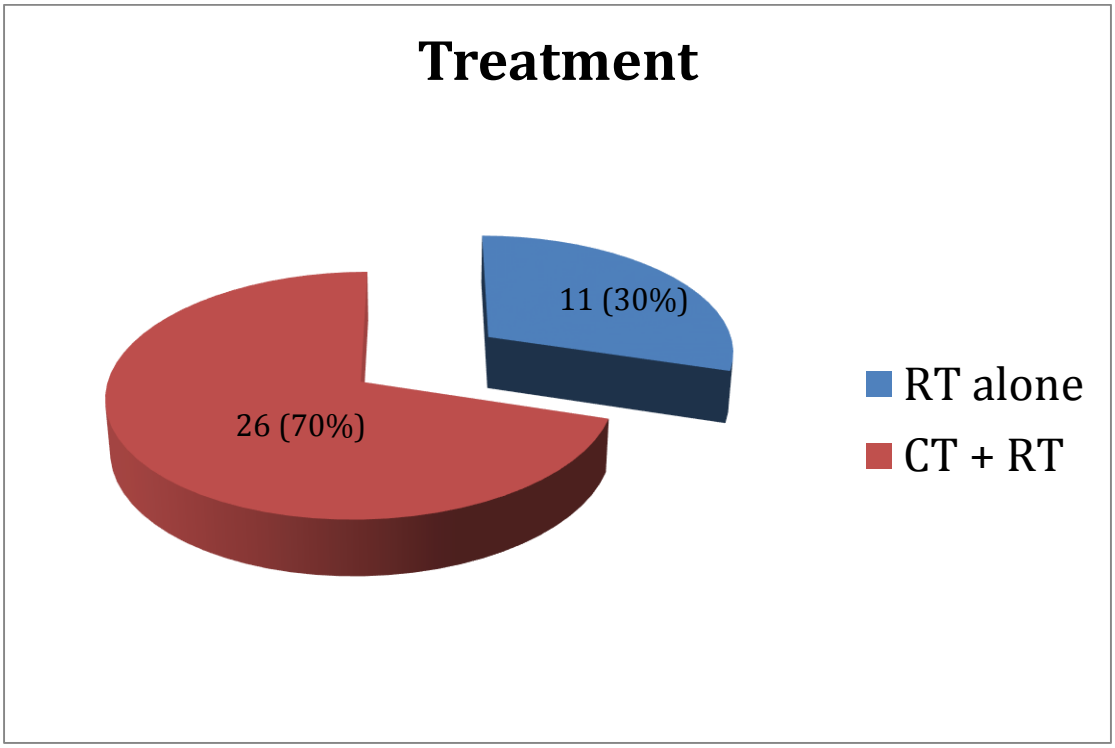
Out of the 37 patients, 18 (49%) were found to be in stage III, 17(46%) in stage IV A and 2(5%) patients belonged to stage IV B.

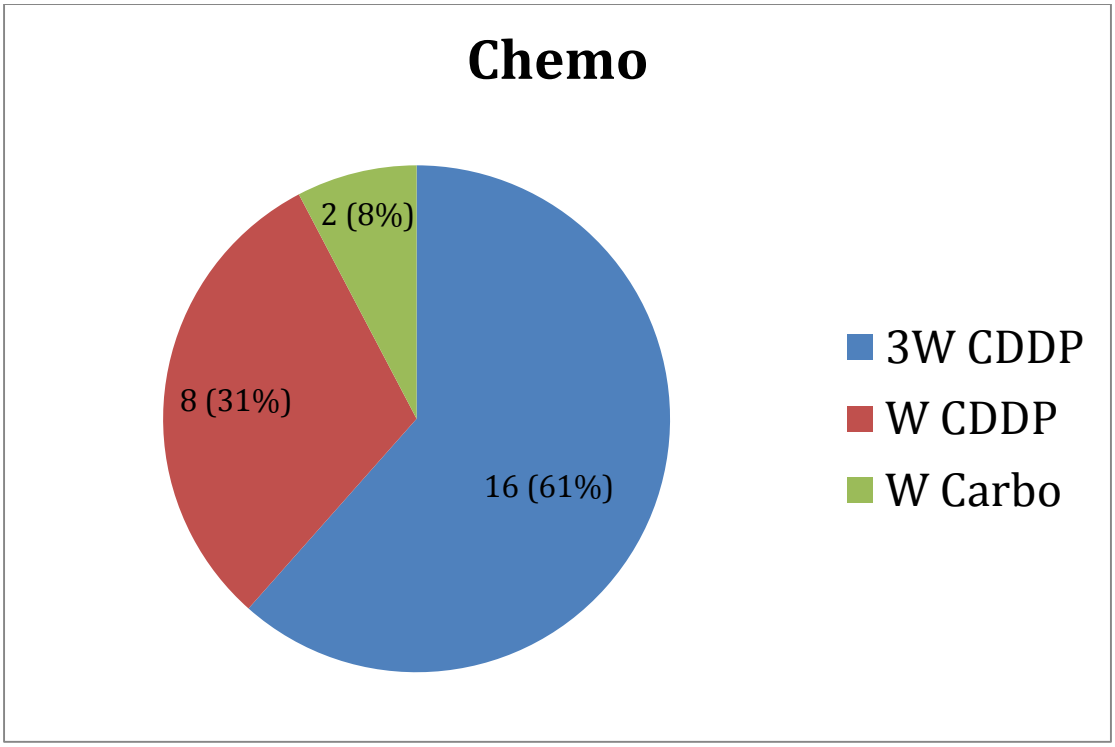
All the characteristics of the patients and tumors are detailed in with pie charts.


Site of primary
7 (19%)
16(43%)
14(38%)
Hypopharynx
Oropharynx
SG larynx


Sex
12
25
Male
Female


Stage
2 (5%)
18 (49%)
17 (46%)
III
IV A
IV B

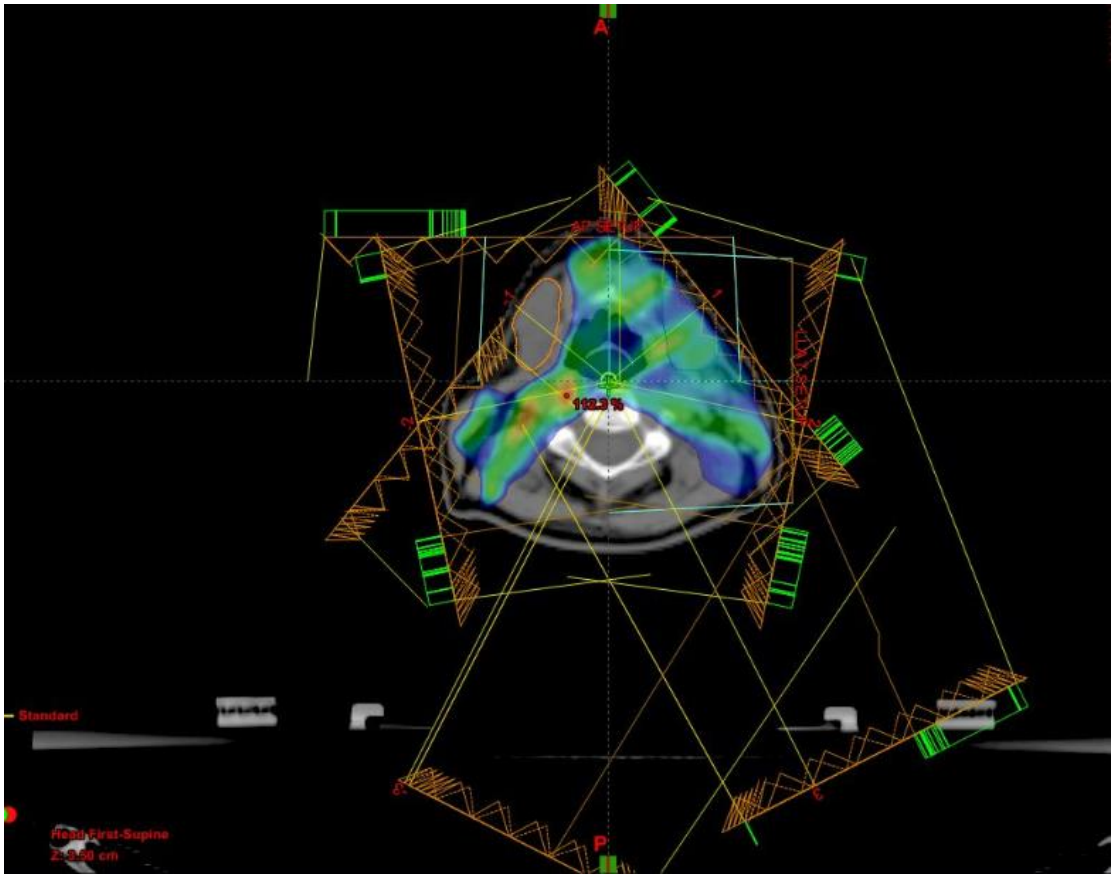

Treatment
11 (30%)
26 (70%)
RT alone
CT + RT


Chemo
2 (8%)
8 (31%)
16 (61%)
3W CDDP
W CDDP
W Carbo

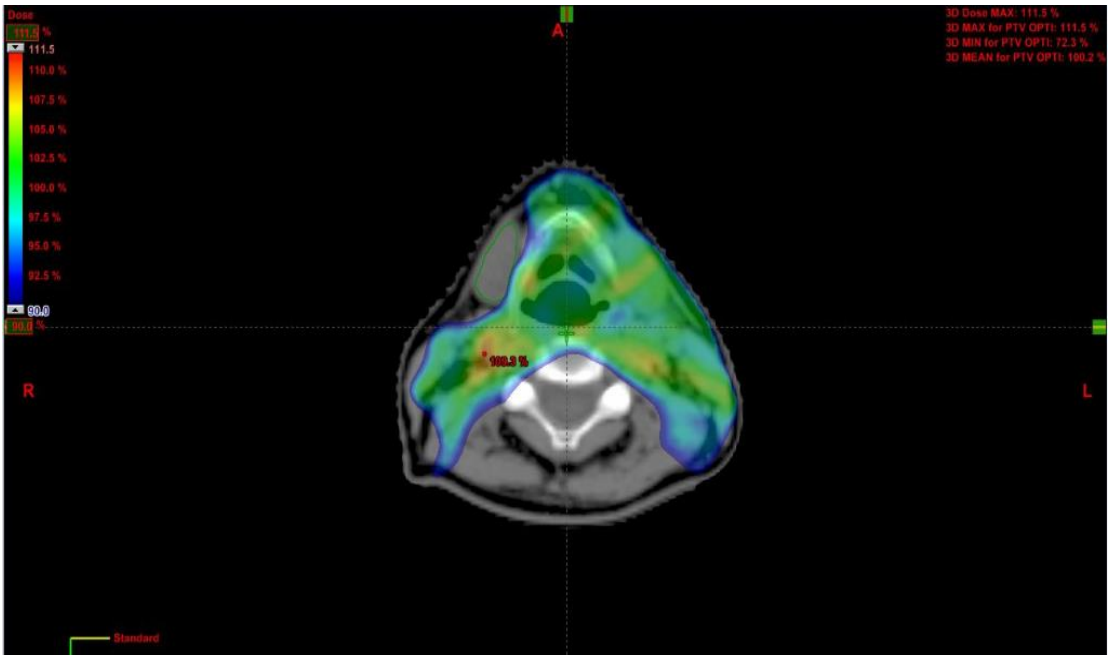
Dose volume characteristics

Ipsilateral parotid	Mean dose (in Gy)
Spared	31
Unspared	30
Contralateral parotid	
Spared	24.2
Unspared	31.9
Ipsilateral SMG	
Spared	60
Unspared	60
Contralateral SMG	
Spared	33
Unspared	60

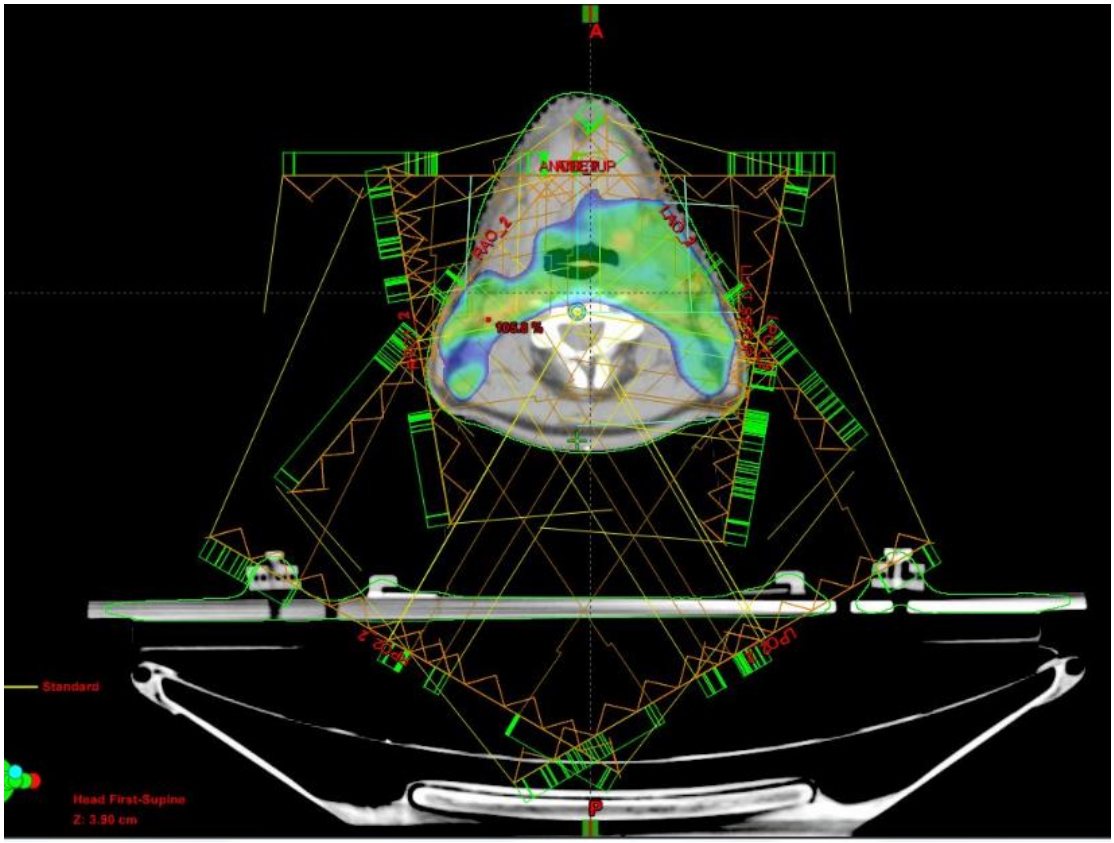
Field alignment in a case of Ca hypopharynx T2 N1 M0 (cSMG spared)



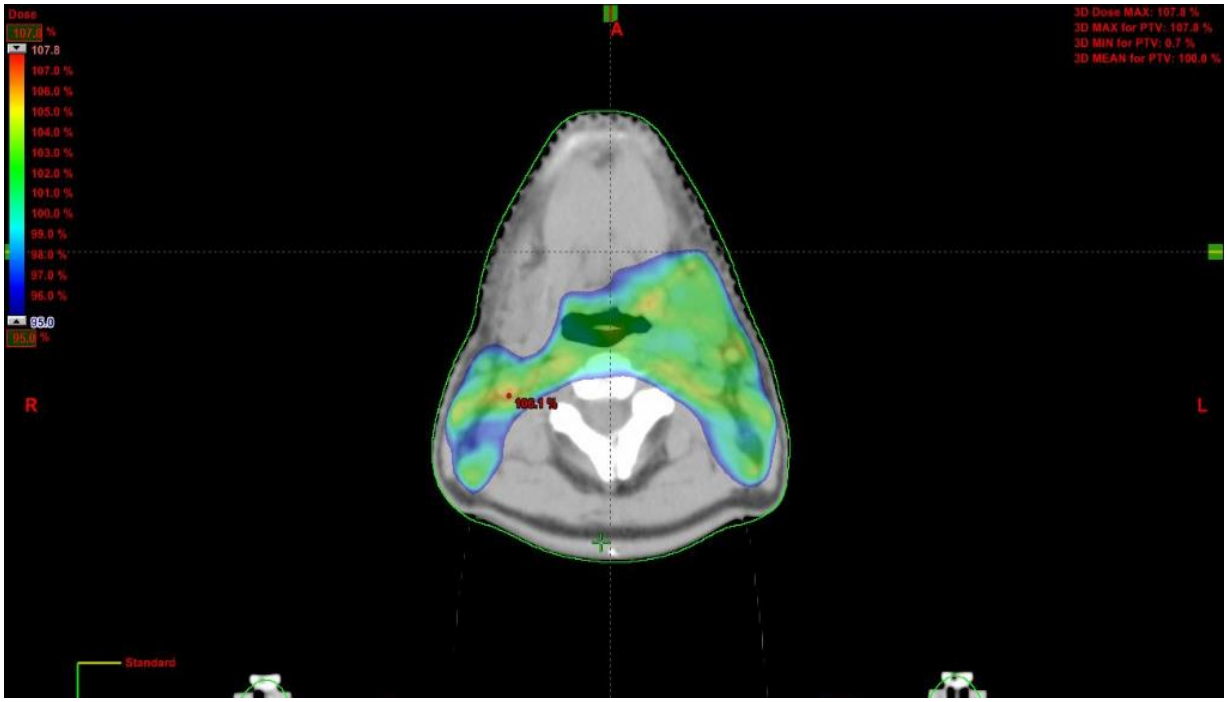
Dose colour wash of the same case as mentioned above



Field alignment in a case of Ca SG larynx T2 N1 M0 (cSMG spared)



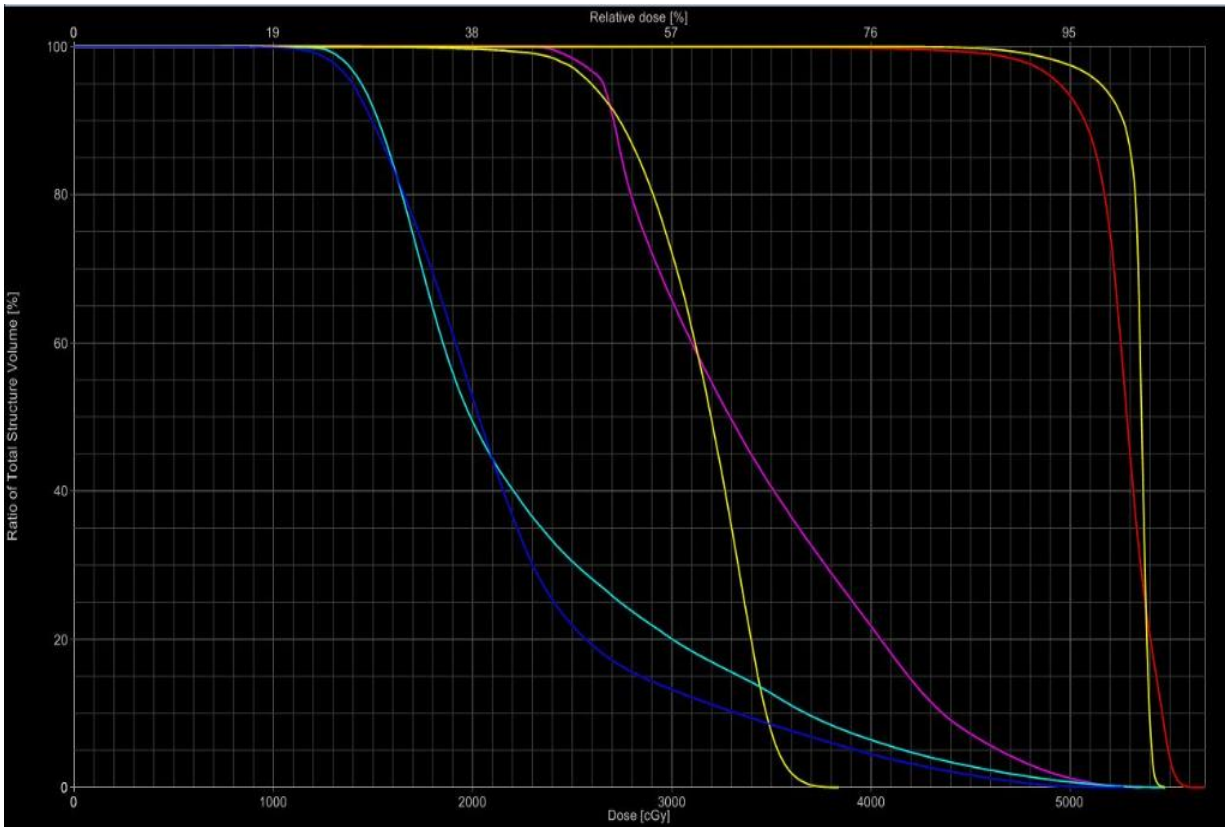
Dose colour wash of the above mentioned plan



This was a case of Ca supraglottic larynx where the growth was in the left aryepiglottic fold extending onto the epiglottis and abutting the left pyriform fossa with left vocal cord fixity.

Clinically, it was Carcinoma SG larynx T3 N0- Stage III

DVH of the above mentioned patient where cSMG spared IMRT was used



Red line- PTV

First yellow line- spine

Dark blue- left parotid

Violet- right SMG

Light blue- right parotid

Second yellow line- left SMG

Assessment of xerostomia

The grading for xerostomia based on the RTOG criteria was done three times. The first time was at the end of treatment where a score of 2 or higher) was seen in 76% of the patients in the cSMG sparing was done against 80% of the control group. There almost no difference at the end of treatment.

At the end of 3 and 6 months from commencement of treatment were 49% and 21% respectively in the study group and, 68% and 54% in the control group. The difference at 6 months was statistically significant ($p < 0.009$)

The xerostomia questionnaire scored by the patients at the end of 6 months showed a mean score of 13 in the study arm against a score of 24 in the control arm. This significant difference was observed due to the lower dryness felt by the patients at rest in the cSMG spared arm.

As mentioned earlier, the questionnaire had two sets of questions which depicted the dryness either at rest or during eating/ chewing. If the score was divided into two sets of questions, the set which corresponded to dryness during chewing/ eating did not show significant difference in both arms, 7 vs 10(from a total score of 20).

But, in the second set of questions which assessed the dryness at rest, the average score in the cSMG spared arm was 6 compared to 14 in the control arm.

Interpretation: This, questionnaire and the result clearly indicates that the resting saliva was better preserved in the cSMG spared arm which resulted in significantly lower scores in the questions related to dryness at rest.

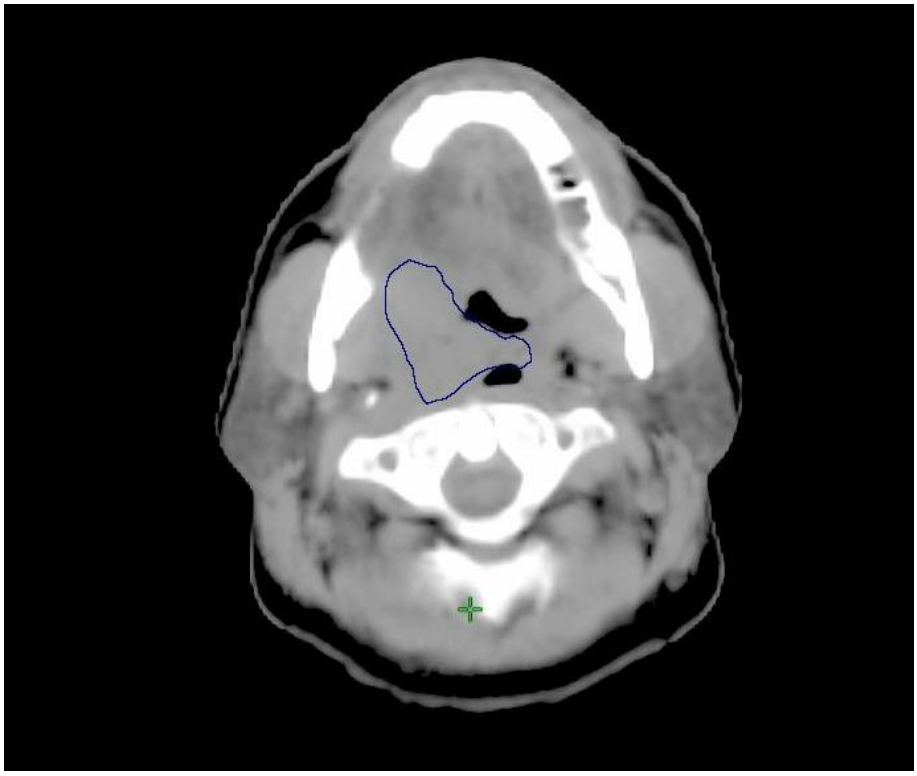
Whereas, although the scores were low for the dryness felt during eating/ chewing in both the arms, there was hardly any difference between the two. This also is justified as in the both the groups, the parotid glands were spared which resulted in preservation of stimulated saliva which is mainly secreted by the parotid gland.

6. DISCUSSION

Although there has been improvement in salivary flow rates by parotid sparing IMRT and it is now considered technique for treating patients with locally advanced head and neck cancers, like hypopharynx and oropharynx, it may still fall short with respect to the patient rated xerostomia. And this has been proved to have a significant impact on quality of life of patients [126, 127, 128, 129].

In the present study, patients treated with cSMG sparing bilateral neck IMRT, the mean dose cSMG could be limited 33Gy. Based on both observer and patient rated xerostomia scores, it was found that xerostomia was significantly lower in the cSMG spared group compared to the control group, independent of parotid sparing.

There are concerns that there could be increase in risk of marginal recurrences with aggressive cSMG sparing as adequate coverage of target volumes could be compromised [130, 131]. There has been a study where recurrences were noted in the area where parotid sparing was done [132]. Hence, the patient selection criteria should be very stringent and is to be followed with utmost care. As, reducing the side effects of treatment is important, it still only plays second fiddle to curing of the disease.



This is a CT cut of a case of Ca oropharynx where the growth is just crossing the midline. This increases the chance of marginal miss and recurrences if cSMG sparing is attempted because of close proximity of the lesion with the level IB region/ submandibular gland.

Though the cSMG sparing could be challenging because of the areas at risk lying in close proximity with the organ that is being attempted to be spared, there have been a number of studies where this has been attempted with no recurrence in the region where the sparing was done.

Study	N	Definitive RT	Mean cSMG dose (Gy)	Disease outcome	Late xerostomia
Univ. of Washington (present report)	76	86%	30.7	No peri-SMG recurrence	23% grade 2+ at 6 months. No permanent grade 3 +.
Helsinki Univ., Finland [24]	50	49%*	27.8	No peri-SMG recurrence	No permanent grade 3+
VU Univ. Med. Ctr., The Netherlands [30]	20	100%	34.1	No peri-SMG nodal recurrence	Not reported
Univ. of Michigan [13]	17†	100%	~43	No contralateral level I recurrence	No grade 3+
Centre Eugene Marquis, France [31]	8	100%	33.8	No peri-SMG recurrence	No grade 3+

The table above shows a list of major studies that have been conducted where cSMG sparing IMRT was used safely.

The most important area on which this study was focussed on was the subjective assessment of xerostomia. This was carried out with a validated Xerostomia Questionnaire developed by the University of Michigan. The results obtained through the patient reported outcomes of the impact dryness had on the QoL indicated that sparing of contralateral submandibular gland resulted in significant improvement in the symptoms.

Few limitations of this study are the small sample size and the non-randomized design which may have lead to some bias. There was also no recording of objective salivary flow measurements to know how it correlated after sparing of the submandibular gland.

However, the observed improvement in both the observer rated xerostoia after 6 months and the patient reported QoL questionnaire show that using the technique of intensity modulation and proper planning, there can be significant reduction in the one of the main side effects of radiation therapy in Head and Neck cancers.

7. CONCLUSION

This was a prospective study where the patients underwent careful selection based on tumor characteristics and were planned using IMRT. The follow up was meticulous and the result obtained showed significant improvement in xerostomia by limiting the dose received by the contralateral submandibular gland along with the parotid.

A multivariate analysis by taking compounding factors with a larger sample size can improve the strength of the study. Longer follow up can also shed light on the recurrence/ failure rates in both the arms. Although it has proven its benefit in improving the QoL of patients, the use of IMRT with daily imaging and time required for careful selection of patients and proper execution of the treatment may lead to questions regarding the time and the cost required for execution of this type of planning. So, it could be worthwhile to do a study which calculates cost/ benefit ratio to better understand the application of this treatment in Indian scenario.

8. REFERENCES

1. Wijers O, Levendag P, Braaksma M, et al. Patients with head and neck cancer cured by radiation therapy: a survey of the dry mouth syndrome in long-term survivors. Head Neck. 2002;24:737–747.

2. Yorke ED, Kutcher GJ, Jackson A, Ling CC. Probability of radiation-induced complications in normal tissues with parallel architecture under conditions of uniform whole or partial organ irradiation. Radiother Oncol 1993;26:226 – 37.

3. Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, Miles EA, Miah AB, Newbold K, Tanay M, Adab F, Jefferies SJ, Scrase C, Yap BK, A'Hern RP, Sydenham MA, Emson M, Hall E: **Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial.** *Lancet Oncol* 2011, **12:**127– 136

4. Jellema AP, Slotman BJ, Doornaert P, Leemans CR, Langendijk JA: Impact of radiation induced xerostomia on quality of life after

primary radiotherapy among patients with head and neck cancer. Int J Radiat Oncol Biol Phys 2007, 69:751–760.

5. Meirovitz A, Murdoch-Kinch CA, Schipper M, Pan C, Eisbruch A: **Grading xerostomia by physicians or by patients after IMRT of head and neck cancer.** *Int J Radiat Oncol Biol Phys* 2006, **66:**445–453.

6. Cawson RA, Gleeson MJ, Eveson JW. The Pathology and Surgery of the Salivary Glands. Oxford, England: Isis Medical Media; 1997.

7. Dawes C. Factors influencing salivary flow rate and composition. In: Edgar M, Dawes C, O'Mullane DM, eds. Saliva and Oral Health. 3rd ed. London: British Dental Association; 2004:32–49.

8. Dawes C. Circadian rhythms in human salivary flow rate and composition. J Physiol 1972;220:529–545.

9. Fischer D, Ship JA. Effect of age on variability of parotid salivary gland flow rates over time. Age Ageing 1999;28:557–561.

10. Parvinen T. Stimulated salivary flow rate, pH and lactobacillus and yeast concentrations in non-smokers and smokers. Scand J Dent Res 1984;92:315–318.

11. Roesink JM, Terhaard CH. The influence of clinical factors on human stimulated parotid flow rate in cancer and other patients. Oral Oncol 2002;38:291–295.

12. Walsh NP, Montague JC, Callow N, Rowlands AV. Saliva flow rate, total protein concentration and osmolality as potential markers of whole body hydration status during progressive acute dehydration in humans. Arch Oral Biol 2004;49:149–154

13. Ship JA, Fischer DJ. Metabolic indicators of hydration status in the prediction of parotid salivary-gland function. Arch Oral Biol 1999;44:343–350.

14.Dawes C. Circadian rhythms in the flow rate and composition of unstimulated and stimulated human submandibular saliva. J Physiol 1975;244:535–548.

15. Dawes C. Rhythms in salivary flow rate and composition. Int J Chronobiol 1974 ;2:253–279.

16. Macgregor ID. Effects of smoking on oral ecology: a review of the literature. Clin Prev Dent 1989;11:3–7.

17. Maier H, Born IA, Mall G. Effect of chronic ethanol and nicotine consumption on the function and morphology of the salivary glands. Klin Wochenschr 1988;66(suppl 11):140–150.

18. Bradley RM. Essentials of Oral Physiology. St. Louis, Mo: Mosby-Year Book, Inc.; 1995.

19. Logemann JA, Smith CH, Pauloski BR, et al. Effects of xerostomia on perception and performance of swallow function. Head Neck 2001;23:317–321.

20. Hamlet S, Faull J, Klein B, et al. Mastication and swallowing in patients with postirradiation xerostomia. Int J Radiat Oncol Biol Phys 1997;37:789–796.

21. Cooper JS, Fu K, Marks J, et al: Late effects of radiation therapy in the head and neck region. Int J Radiat Oncol Biol Phys 31:1141-1164, 1995

22. Balogh JM, Sutherland SE: Osteoradionecrosis of the mandible: A review. J Otolaryngol 18:245-250, 1989

23. Korsten MA, Rosman AS, Fishbein S, et al: Chronic xerostomia increases esophageal acid exposure and is associated with esophageal injury. Am J Med 90:701-706, 1991

24. Kagami H, Hiramatsu Y, Hishida S, et al: Salivary growth factors in health and disease. Adv Dent Res 14:99-102, 2000

25. Awidi A, Homsi U, Kakail AI, et al: Double blind, placebo controlled cross-over study of oral pilocarpine for the prevention of chemotherapy-induced oral mucositis in adult patients with cancer. Eur J Cancer 37:2010-2014, 2001.

26. Franzen L, Funegard U, Ericson T, Henriksson R. Parotid gland function during and following radiotherapy of malignancies in the head and neck: a consecutive study of salivary flow and patient discomfort. Eur J Cancer. 1992;28:457–462.

27. Burlage FR, Coppes RP, Meertens H, Stokman MA, Vissink A. Parotid and submandibular/sublingual salivary flow during high dose radiotherapy. Radiother Oncol 2001;61:271–274

28. Valdez IH, Atkinson JC, Ship JA, Fox PC. Major salivary gland function in patients with radiation-induced xerostomia: flow rates and sialochemistry. Int J Radiat Oncol Biol Phys 1993;25:41–47.

29. Price RE, Ang KK, Stephens LC, Peters LJ. Effects of continuous hyperfractionated accelerated and conventionally fractionated

radiotherapy on the parotid and submandibular salivary glands of rhesus monkeys. Radiother Oncol 1995;34:39–46

30. Nagler RM. Effects of head and neck radiotherapy on major salivary glands—animal studies and human implications. In Vivo 2003;17:369–375.

31. Koukourakis MI, Kyrias G, Kakolyris S, et al. Subcutaneous administration of amifostine during fractionated radiotherapy: a randomized phase II study. J Clin Oncol 2000;18:2226–2233.

32. Bergonie J. Sur quelques formes de reactions precoses apresdes irradiations [in French]. Arch ElectMed. 1911;19:241–245

33. Abok K, Brunk U, Jung B, et al. Morphologic and histochemical studies of the deferring radiosensitivity of the ductular and acinar cell of the rat submandibular gland. Virchows Arch Cell Pathol. 1984;45:443–460.

34. Roesink J,MoerlandM, Hoekstra A, et al. Scintigraphic assessment of early and late parotid gland function after radiotherapy for head-and-neck cancer: a prospective study of dosevolume\ response relationships. Int J Radiat Oncol Biol Phys.2004;58:1451–1460.

35. Konings A, Coppes R, Vissink A. On the mechanism of salivary gland radiosensitivity. Int J Radiat Oncol Biol Phys. 2005;62:1187–1194.

36. Valdez I. Radiation-induced salivary dysfunction: clinical course and significance. Special Care Dent. 1991;11:525–255.

37. Eneroth C, Henrikson C, Jacobson P. Effect of fractionated radiotherapy on salivary gland function. Cancer. 1972;30:1147–1153.

38. Roesink J, Moerland M, Battermann J, et al. Quantitative dose-volume response analysis of changes in parotid gland function after radiotherapy in the head-and-neck region. Int J Radiat Oncol Biol Phys. 2001;51:938–946.

39. Braam P, Roesink J, Moerland M, et al. Long-term parotid gland function after radiotherapy. Int J Radiat Oncol Biol Phys. 2005;62:659–664.

40. Eisbruch A, Terrell J. The relationship between xerostomia and dysphagia after chemoradiation of head and neck cancer. Head Neck. 2003;25:1082; author reply, 1082–1083.

41. Mossman KL: Quantitative radiation dose-response relationships for normal tissue in man. II. Response of the salivary glands during radiation. Radiat Res 95:392-398, 1983

42. Ship JA, Eisbruch A, D'Hondt E, et al: Parotid sparing study in head and neck cancer patients receiving radiation therapy: One-year results. Dent Res 76:807-813, 1997

43. Shannon IL, Trodhal JN, Starcke EN: Radiosensitivity of the human parotid gland. Proc Soc Exp Biol Med 157:50-53, 1978

44. Kashima HK, Kirkham WR, Andrews JR: Postirradiation sialadenitis. Am J Roent Radium Ther Nucl Med 94:271-291, 1965

45. Stephens LC, Ang KK, Schultheiss TE, et al: target cell and mode of radiation injury in rhesus salivary glands. Radiother Oncol 7:165-174, 1986.

46. Savage NW, Kruger BJ, Adkins KF: The effects of fractionated megavoltage irradiation on rat salivary glands: An assessment by electron microscopy. Aust Dent J 30: 188-193, 1985

47. Tsuji H: Quantitative dose-response analysis of salivary function following radiotherapy using sequential RI- sialography. Int J Radiat Oncol Biol Phys 11:1603-1612, 1985.

48. Van Acker F, Flamen P, Lambin P, et al: The utility of SPECT in determining the relationship between radiation dose and salivary gland dysfunction after radiotherapy. Nucl Med Commun 11:225-231, 2001.

49. Ericson S: An investigation of human parotid saliva secretion rate in response to different type of stimulants. Arch Oral Biol 14:591-594, 1969.

50. Mandel ID: Sialochemistry in disease and clinical situations affecting salivary glands. Crit Rev Clin Lab Sci, 12:321-366, 1980.

51. Holmes JH: Changes in salivary flow produced by changes in fluid and electrolyte balance, in Sreebny LM, Meyer J(eds). Salivary Glands and Their Secretions. New York, NY, MacMillan Co, 1964, pp 177-195

52. Eisbruch A, Kim HM, Ten Haken R, et al: Dose, volume and function relationships in parotid glands following conformal and intensity modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 45:577-587, 1999.

53. Navazesh M: Methods for collecting saliva. Ann. NY Acad Sci 694:72-77, 1993

54. O'Connell AC: Natural history and prevention of radiation injury. Adv Dent Res 14:57-61, 2000

55. LENT SOMA Tables. Radiother Oncol 35:17-60, 1995

56. Eisbruch A, Kim HM, Terrell JE, et al: Xerostomia and its predictors following parotid-sparing irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 50:695-704, 2001

57. Wasserman T, Macowiac JI, Brizel DM, et al: Effect of amifostine on patient assessed clinical benefit in irradiated head and neck cancer. Int J Radiat Oncol Biol Phys 48:1035-1039, 2000

58. Fox PC, Busch KA, Baum BJ: Subjective reports of xerostomia and objective measures of salivary gland performance. J Am Dent Assoc 115:581-584, 1987

59. Bjordal K, Kaas S: Psychometric validation of the EORTC core quality of life questionnaire and a diagnosis specific module for head and neck cancer patients. Acta Oncol 31:311-321, 1992

60. Hassan SJ, Weymuller EAL: Assessment of quality of life in head and neck cancer patients. Head Neck 15:485-496, 1993

61. Browman GP, Levine MN, Hodson DI, et al: The head and neck radiotherapy questionnaire: A morbidity/quality of life instrument for clinical trials of radiation therapy in head and neck cancer. J Clin Oncol 11:863-872, 1993

62. Cella DF, Bonomi AE: Measuring quality of life: 1995 update. Oncology 9:47-60, 1995 (suppl)

63. Terrell JE, Nanavati KA, Esclamado RM, et al: Head and neck cancer-specific quality of life: Instrument validation. Arch Otolaryngol Head Neck Surg 124:964-971, 1998

64. Trotti A, Johnson DJ, Gwede C: Development of a head and neck companion module for the quality of life–radiation therapy instrument. Int J Radiat Oncol Biol Phys 42:257-261, 1998

65. Eisbruch A, Kim HM, Terrell JE, et al: Xerostomia and its predictors following parotid-sparing irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys 50:695-704, 2001

66. Lee N, Xia P, Quivey JM, et al: Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: An update of the UCSF experience. Int J Radiat Oncol Biol Phys 53:12-22, 2002

67. Epstein J, Emerton S, Kolbinson D, et al. Quality of life and oral function following radiotherapy for head and neck cancer. Head Neck. 1999;21: 1–11.

68. Hamlet S, Faull J, Klein B, et al. Mastication and swallowing in patients with post-irradiation xerostomia. Int J Radiat Oncol Biol Phys. 1997;37:789–796.

69. Logemann J, Pauloski B, Rademaker A, et al. Xerostomia: 12-month changes in saliva production and its relationship to perception and performance of swallow function, oral intake and diet after chemoradiation. Head Neck. 2003;25:432–437.

70. Kendall K, McKenzie S, Leonard R, Jones C. Structural mobility in deglutition after single modality treatment of the head and neck carcinomas with radiotherapy. Head Neck. 1998;20: 720–725.

71. Rhodus N,Moller K, Colby S, Bereuter J. Dysphagia in patients with three different etiologies of salivary gland dysfunction Ear Nose Throat J. 1995;74:39–42.

72. Kendall K, McKenzie S, Leonard R, Jones C. Timing of swallowing events after single-modality treatment of head and

neck carcinomas with radiotherapy. Ann Otol Rhinol Laryngol. 2000;109: 767–775.

73. Lazarus C. Effects of radiation therapy and voluntary manoeuvres on swallow functioning in head and neck cancer patients. Clin Commun Disord. 1993;3:11–20.

74. Logemann J, Smith C, Pauloski B, et al. Effects of xerostomia on perception and performance of swallow function. Head Neck. 2001;23:317–321.

75. Nelson G. Biology of taste buds and the clinical problem of taste loss. Anat Rec. 1998;253:70–78.

76. Maes A, Huygh I, Weltens C, et al. De gustibus: time scale of loss and recovery of tastes caused by radiotherapy. Radiother Oncol. 2002;63:195–201.

77. Rhodus N, Moller K, Colby S, Bereuter J. Articulatory speech performance in patients with salivary gland dysfunction: a pilot study. Quintessence Int. 1995;26:805–810.

78. Roh J, Kim A, Cho M, et al. Xerostomia following radiotherapy of the head and neck affects vocal function. J Clin Oncol. 2005;23:3016–3023.

79. Meyer T, Kuhn J, Campbell B, et al. Speech intelligibility and quality of life in head and neck survivors. Laryngoscope. 2004;114:1977–1981.

80. Tatum R, Daniels R. The correlation of radiotherapy to salivary gland reduction and increased caries incidence: a caries control method. Quintessence Int. 1982;13: 9–11.

81. Joyston-Bechal S, Hayes K, Davenport E, Hardie J. Caries incidence, mutans Streptococci and Lactobacilli in irradiated patients during a 12-month preventive programme using chlorhexidine and fluoride. Caries Res. 1992;26: 384–390.

82. Spak C, Johnson G, Ekstrand J. Caries incidence, salivary flow rate and efficacy of fluoride gel treatment in irradiated patients. Caries Res. 1994;28: 388–393.

83. Kumar H, Bihani V, Kumar V, et al. Osteoradionecrosis of the mandible in patients treated with definitive radiotherapy for carcinomas of oral cavity and oropharynx. A retrospective study. Indian J Dent Res. 1992;3:47–50.

84. Specht L. Oral complications in the head and neck radiation patient. Introduction and scope of the problem. Support Care Cancer. 2002;10: 36–39.

85. Sonis S, Fey E. Oral complications of cancer therapy. Oncology. 2002;16: 680–686.

86. Beeken L, Calman F. A return to ‘normal eating’ after curative treatment for oral cancer. What are the long-term prospects? Eur J Cancer B Oral Oncol. 1994;30: 387–392.

87. Fang F, Liu Y, Tang Y, et al. Quality of life as a survival predictor for patients with advanced head and neck carcinoma treated with radiotherapy. Cancer. 2003;100 :425–432.

88. Giatromanolaki A, Sivridis E, Maltezos E, Koukourakis M. Down-regulation of intestinal-type alkaline phosphatase in the tumor vasculature and stroma provides a strong basis for explaining amifostine selectivity. Semin Oncol. 2002;29:14–21.

89. McChesney S, Gillette E, Dewhirst M, Withrow S. Influence of WR 2721 on radiation response of canine soft tissue sarcomas. Int J Radiat Oncol Biol Phys. 1986;12:1957–1963.

90. Thompson D, Wyrick S, Holbrook D, Chaney S. Effect of the chemoprotective agent WR-2721 on disposition and biotransformations of ormaplatin in the Fischer 344 rat bearing a fibrosarcoma. Cancer Res. 1995;55:2837–2846.

91. Andreassen C, Grau C, Lindegaard J. Chemical radioprotection: a critical review of amifostine as a cytoprotector in radiotherapy. Semin Radiat Oncol. 2003;13:62–72.

92. Brizel D, Wasserman T, Henke M, et al. Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. J ClinOncol. 2000;18:3339–3345.

93. Wasserman T, Brizel D, Henke M, et al. Influence of intravenous amifostine on xerostomia, tumor control and survival after

radiotherapy for head-and-neck cancer: a 2-year followup of a prospective, randomized, phase III trial. Int J Radiat Oncol Biol Phys. 2005;63:985–990.

94. Sasse A, De Oliviera Clark L, Sasse E, Camara C. Amifostine reduces side effects and improves complete response rates during radiotherapy: results of a meta-analysis. Int J Radiat Oncol Biol Phys. 2006;64:784–791.

95. Brizel D, Overgaard J. Does amifostine have a role in chemoradiation treatment? Lancet Oncol. 2003;4:378–381.

96. Buentzel J, Micke O, Adamietz I, et al. Intravenous amifostine during chemoradiotherapy for head-and-neck cancer: a randomized\ placebo-controlled phase III study. Int J Radiat Oncol Biol Phys. 2006;64:684–691.

97. Anne P, Curran W. A phase II trial of subcutaneous amifostine and radiation therapy in patients with head and neck cancer. Semin Radiat Oncol. 2002;12:18–19.

98. Jha N, Seikaly H,McGaw T, Coulter L. Submandibular salivary gland transfer prevents radiation-induced xerostomia. Int J Radiat Oncol Biol Phys. 2000;46:7–11

99. Seikaly H, Jha N, McGaw T, et al. Submandibular gland transfer: a new method of preventing radiation-induced xerostomia. Laryngoscope. 2001;111:347–352.

100. Jha N, Seikaly H, Harris J, et al. Prevention of radiation induced xerostomia by surgical transfer of submandibular salivary gland into the submental space. Radiother Oncol. 2003;66: 283–289

101. Seikaly H, Jha N, Harris J, et al. Long-term outcome of submandibular gland transfer for prevention of postradiation xerostomia.
Arch Otolaryngol Head Neck Surg. 2004;130:956–961.

102. Pathak K, Bhalavat R, Mistry R, et al. Upfront submandibular salivary gland transfer in pharyngeal cancers. Oral Oncol. 2004;40:960–963.

103. Liu X, Zeng Z, Hong M, et al. Primary effect of submandibular salivary gland transfer in preventing radiation-induced xerostomia of nasopharyngeal carcinoma. Ai Zheng. 2005;24:577–581.

104. Maes A, Weltens C, Flamen P, et al. Preservation of parotid function with uncomplicated conformal radiotherapy. Radiother Oncol. 2002;63:203–211.

105. Eisbruch A, Ship J, Martel M, et al. Parotid gland sparing in patients undergoing bilateral head and neck irradiation: techniques and early results. Int J Radiat Oncol Biol Phys. 1996;36: 469–480.

106. Chao KSC, Majhail N, Huang C, et al. Intensity-modulated radiation therapy reduces late salivary toxicity without compromising tumor control rates in patients with ororpharyngeal carcinoma: a comparison with conventional techniques. Radiother Oncol. 2001;61:275–280.

107. Saarilahti K, Kouri M, Collan J, et al. Intensity modulated radiotherapy for head and neck cancer: evidence of preserved salivary gland function. Radiother Oncol. 2005;74:251–258.

108. Pacholke H, Amdur R, Morris C, et al. Late xerostomia after intensity-modulated radiation therapy versus conventional radiotherapy. Am J Clin Oncol. 2005;28: 351–358

109. Lin A, Kim H, Terrell J, et al. Quality of life after parotid-sparing IMRT for head-and-neck cancer: a prospective longitudinal study. Int J Radiat Oncol Biol Phys. 2003;57:61–70.

110. Jabbari S, Kim H, Feng M, et al. Matched case-control study of quality of life and xerostomia after intensity-modulated radiotherapy or standard radiotherapy for head-and-neck cancer: initial report. Int J Radiat Oncol Biol Phys. 2005;63: 725–731.

111. Chao KSC, Deasy J, Markman J, et al. A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results. Int J Radiat Oncol Biol Phys. 2001;49:907–916.

112. Eisbruch A, Ten Haken R, Kim H, et al. Dose, volume and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. Int J Radiat Oncol Biol Phys. 1999;45:577–587.

113. Blanco AI, Chao KSC, El Naqa I, et al. Dose-volume modelling of salivary function in patients with head-and-neck cancer receiving radiotherapy. Int J Radiat Oncol Biol Phys. 2005;62: 1055–1069.

114. Munter M, Karger C, Hoffner S, et al. Evaluation of salivary gland function after treatment of head-and-neck tumors with intensity-modulated radiotherapy by quantitative pertechnetate scintigraphy. Int J Radiat Oncol Biol Phys. 2004;58:175–184.

115. Chambers S, Garden AS, Rosenthal D, et al. Intensity-modulated radiotherapy: is xerostomia still prevalent? Curr Oncol Rep. 2005;7:131–136.

116. Lindberg R: Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. *Cancer* 1972, 29:1446–1449.

117. Brekel van den NWM, Stel HV, Castelijns JA, et al: Cervical lymph node metastasis: Assessment of radiologic criteria. Radiology 177:379-384, 1990

118. Mukherji SK, Armao D, Joshi VM: Cervical nodal metastases in squamous cell carcinoma of the head and neck: What to expect. Head Neck Surg 23:995-1005, 2001

119. Rouviere H: Lymphatic Systems of the Head and Neck (Tobias MJ, trans.). Ann Arbor, MI, Edwards Brothers, 1938

120. Eisbruch A, Foote RL, O'Sullivan B, et al. Intensity-modulated radiation therapy for head and neck cancer: Emphasis on the selection and delineation of the targets. Semin Radiat Oncol 2002; 12:238–249.

121. Wijers OB, Levendag PC, Tan T, et al: A simplified CT-based definition of the lymph node levels in the node negative neck. Radiother Oncol 52:35-42, 1999

122. Eisbruch A, Kim HM, Terrell JE, *et al.* Xerostomia and its predictors following parotid-sparing irradiation of head and neck cancer. *Int J Radiat Oncol Biol Phys* 2001;50:695–704.

123. Jabbari S, Kim HM, Feng M, *et al.* Quality of life and xerostomia following standard vs. intensity modulated irradiation: A matched case-control comparison. *Int J Radiat Oncol Biol Phys* 2005;63:725–731.

124. Lin A, Kim HM, Terrell JE, *et al.* Quality of life following parotid-sparing IMRT of head and neck cancer: A prospective longitudinal study. *Int J Radiat Oncol Biol Phys* 2003; 57:61–70.

125. Pacholke HD, Amdur RJ, Morris CG, *et al.* Late xerostomia after intensity-modulated radiation therapy versus conventional radiotherapy. *Am J Clin Oncol* 2005;28:351–358.

126. Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, Miles EA, Miah AB, Newbold K, Tanay M, Adab F, Jefferies SJ, Scrase C, Yap BK, A'Hern RP, Sydenham MA, Emson M, Hall E: Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. *Lancet Oncol* 2011, 12:127–136.

127. Kam MKM, Leung S, Zee B, Chau RM, Suen JJ, Mo F, Lai M, Ho R, Cheung KY, Yu BK, Chiu SK, Choi PH, Teo PM, Kwan WH, Chan AT: Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage

nasopharyngeal carcinoma patients. *J Clin Oncol* 2007, 25:4873–4879.

128. Jellema AP, Slotman BJ, Doornaert P, Leemans CR, Langendijk JA: Impact of radiation induced xerostomia on quality of life after primary radiotherapy among patients with head and neck cancer. *Int J Radiat Oncol Biol Phys* 2007, 69:751–760. 10.

129. Meirovitz A, Murdoch-Kinch CA, Schipper M, Pan C, Eisbruch A: Grading xerostomia by physicians or by patients after IMRT of head and neck cancer. *Int J Radiat Oncol Biol Phys* 2006, 66:445–453.

130. Eisbruch A: Reducing xerostomia by IMRT: what may, and may not, be achieved. *J Clin Oncol* 2007, 25:4863–4864.

131. Mendenhall WM, Mendenhall CM, Mendenhall NP: Submandibular gland-sparing intensity-modulated radiotherapy. *Am J Clin Oncol*. in press.

132. Cannon DM, Lee NY: Recurrence in region of spared parotid gland after definitive intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys* 2008, 70:660–665.

133. Little M, Schipper M, Feng FY, Vineberg K, Cornwall C, Murdoch-Kinch CA, Eisbruch A: Reducing xerostomia after

chemo IMRT for head-and-neck cancer: beyond sparing the parotid glands. *Int J Radiat Oncol Biol Phys* 2012, 83:1007–1014.

134. Chajon E, Lafond C, Louvel G, Castelli J, Williaume D, Henry O, Jégoux F, Vauléon E, Manens JP, Le Prisé E, de Crevoisier R: Salivary gland-sparing other than parotid sparing in definitive head-and-neck intensity-modulated radiotherapy does not seem to jeopardize local control. *Radiat Oncol* 2013, 8:132.

135. Defining the risk of involvement for each neck nodal level in patients with early T-stage node-positive oropharyngeal carcinoma. Sanguineti G, Califano J, Stafford E, Fox J, Koch W, Tufano R, Sormani MP, Forastiere A Int J Radiat Oncol Biol Phys. 2009 Aug 1; 74(5):1356-64.[PubMed] [Ref list]

136. Gensheimer MF, Liao JJ, Garden AS, Laramore GE, Parvathaneni U, et al. Submandibular gland-sparing radiation therapy for locally advanced oropharyngeal squamous cell carcinoma: patterns of failure and xerostomia outcomes. Radiat Oncol. 2014;9: 255.